2018-01-31

Prenatal maternal psychosocial stress and offspring's asthma and allergic disease : a systematic review and meta-analysis

Flanigan, Catherine; Sheikh, Aziz; DunnGalvin, Audrey; Brew, Bronwyn K; Almqvist, Catarina; Nwaru, Bright I

Clin Exp Allergy. 2018 Apr;48(4):403-414.
Wiley
http://doi.org/10.1111/cea.13091
http://hdl.handle.net/10616/46210

Prenatal maternal psychosocial stress and offspring's asthma and allergic disease: a systematic review and meta-analysis

Flanigan, Catherine; Sheikh, Aziz; DunnGalvin, Audrey; Brew, Bronwyn K; Almqvist, Catarina; Nwaru, Bright I

DOI: 10.1111/cea.13091

Prenatal maternal psychosocial stress and offspring's asthma and allergic disease: a systematic review and meta-analysis

Catherine Flanigan,[1] Aziz Sheikh,[1] Audrey DunnGalvin,[2-4] Bronwyn K Brew,[5] Catarina Almqvist,[5,6] Bright I Nwaru[1,7-9]

[1]Asthma UK Centre for Applied Research, Centre for Medical Informatics, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK
[2]Department of Paediatrics and Child Health, Cork University Hospital, Cork City Ireland
[3]University College Cork, Cork City, Ireland
[4]School of Applied Psychology, University College Cork, Cork City, Ireland
[5]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden
[6]Pediatric Allergy and Pulmonology Unit at Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden
[7]Krefting Research Centre, Institute of Medicine, University of Gothenburg, Sweden
[8]Wallenberg Centre for Molecular and Translational Medicine, Institute of Medicine, University of Gothenburg, Sweden
[9]School of Health Sciences, University of Tampere, Finland

Correspondence
Bright I Nwaru
Krefting Research Centre
Institute of Medicine
University of Gothenburg
SE-405 30 Gothenburg, Sweden
Email: bright.nwaru@gu.se
Tel : +46 317 866 718

Keywords: adverse life events, allergy, asthma, children, pregnancy, psychosocial stress
Running head: Prenatal stress and offspring asthma and allergy disease

Word count:
Main text: 3901
Abstract: 301
Number of References: 59

ABSTRACT

Background: Prenatal maternal stress may influence offspring's atopic risk through sustained cortisol secretion resulting from activation of the hypothalamic-pituitary-axis (HPA), leading to Th2-biased cell differentiation in the fetus. We undertook a systematic review and meta-analysis investigating the relationship between prenatal maternal psychosocial stress and risk of asthma and allergy in the offspring.

Design:

Methods: We searched 11 electronic databases from 1960 to 2016, search the grey literature, and contacted experts in the field. Type of stress indicator included mood disorders, anxiety, exposure to violence, bereavement and socio-economic problems occurring during pregnancy, both objectively or subjectively measured. We included all possible asthma and IgE-mediated allergy outcomes. We conducted random-effects meta-analyses to synthesize the data.

Results: We identified 9,779 papers of which 30 studies (enrolling >6 million participants) satisfied inclusion criteria. The quality of 25 studies was moderate, four were strong, and one was weak. Maternal exposure to any type of stressors was associated with an increased risk of offspring atopic eczema/dermatitis (OR 1.34, 95%CI 1.22-1.47), allergic rhinitis (OR 1.30, 95%CI 1.04-1.62), wheeze (OR 1.34, 95%CI 1.16-1.54) and asthma (OR 1.15, 95%CI 1.04-1.27). Exposure to anxiety and depression had strongest effect compared to other stressors. Exposure during the third trimester had the greatest impact compared to first and second trimesters. The increased risk was stronger for early-onset and persistent than for late-onset wheeze. Bereavement of a child (HR 1.28, 95%CI 1.10-1.48) or a spouse (HR 1.40, 95%CI 1.03-1.90) increased the risk of offspring asthma.

Conclusions: Exposure to prenatal maternal psychosocial stress was associated with increased risk, albeit modestly, of asthma and allergy in the offspring. The pronounced risk during the third trimester may represent cumulative stress exposure throughout pregnancy rather than trimester-specific effect. Our findings may represent a causal effect or a result of inherent biases in studies, particularly residual confounding.

Systematic review registration: PROSPERO (2016:CRD42016036456)

INTRODUCTION

The susceptibility to develop asthma and allergy may be established already in utero.[1-4] The concept of fetal programming has provided important insights on the influence of the intrauterine environment on the development of the fetus and subsequent[5] risk of chronic conditions later in life.[6] As adaptive immunity develops prenatally, allergen specific immune responses are demonstrable in newborns[2,3,7] with umbilical cord blood shown to contain fetally derived immunoglobulin E (IgE).[1,3]

One suggested pathway through which prenatal maternal stress may influence the risk of asthma and allergy in the offspring is through the activation of the hypothalamic-pituitary-axis (HPA) in response to external stress.[8,9] This then causes secretion of hormones by the hypothalamus and pituitary gland in the brain and subsequent stimulation of the release of glucocorticoids, adrenaline and noradrenaline.[8-10] The release of glucocorticoids leads to increases in cortisol levels.[8,9] The activities of the HPA and the resultant chemical reactions can be transmitted to the fetus and thus influences development.[6,11] High levels of cortisol increase airway responsiveness in the offspring and potentiated cell differentiation from T helper cell type 1 (Th1) to T helper cell type 2 (Th2) phenotypes.[12] Maternal stress can also lead to a decrease in the glutathione/glutathione disulfide (GSSG) ratio, leading to oxidative stress and subsequent risk of asthma in the offspring.[8,9]

Several epidemiologic studies investigating indicators of prenatal maternal psychosocial stress on the risk of asthma and allergy in the offspring show that maternal exposure to stress may increase the risk of asthma and allergy in the offspring. Although two recent systematic reviews summarized existing studies,[13,14] a comprehensive synthesis of the underlying evidence is lacking. In the first review, only wheeze and asthma outcomes were considered.[13] Although the second review included the full spectrum of allergy outcomes, the searches were confined to a limited number of databases and only a narrative synthesis was perfomed.[14] Since the publication of these reviews, there have been a number of additional studies published. To provide a clearer and comprehensive picture of the underlying evidence, we undertook a systematic review with meta-analysis of studies that have investigated the association between prenatal maternal exposure to psychosocial stress and the risk of asthma and allergy in the offspring. We included the full spectrum of asthma and allergy outcomes and were also interested in understanding whether the type of indicator of prenatal psychosocial stress and timing (trimester) of exposure were important.

METHODS

We published[15] and registered in PROSPERO (registration number: 2016:CRD42016036456) the protocol for the review prior to commencement of the systematic review, which outlined the approaches to undertaking the review.

Study types

Experimental studies (i.e. randomized-controlled trials, quasi-randomized controlled trials, controlled-clinical trials, controlled before-and-after studies, interrupted time-series designs) and analytical epidemiological studies (cohort, case-control, and cross-sectional studies) were eligible for inclusion. We excluded reviews, case-studies, case-series, and animal studies.

Participants

Pregnant women and their offspring of any age.

Exposure

We included all indicators of psychosocial stress, mood states, and acute or chronic stressors or negative life events (NLEs), including: anxiety and depression, issues with existing children, exposure to violence, discrimination or prejudice, financial problems, residential move or housing issues, daily stressors or generalized psychological distress, bereavement, natural disasters, separation, divorce or marital problems, involuntary job loss for mother or partner, and homelessness. We included studies with either objectively-measured or subjectively-reported measures of the stress events.

Outcomes

Primary outcomes were: asthma, atopic dermatitis/eczema, atopic sensitization, food allergy, allergic rhinitis, urticaria and anaphylaxis. All primary outcomes, with the exception of atopic sensitization, were defined either by physician assessment or by the self-report. Additionally, asthma diagnosis through use of airway function tests including peak expiratory flow [PEF], forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], forced expiratory flow rate or alternative age appropriate pulmonary function tests [oscillometry or exhaled nitric oxide analysis] were also accepted methods of assessment. Secondary outcomes included: asthma exacerbations, use of asthma medications, hospitalization for asthma, wheeze as defined by self-report or physician diagnosis, and measures of Health Related Quality of Life (HRQoL).

Study identification

We searched the following databases from 1960 to the end of 2016: MEDLINE, EMBASE, Cochrane Library, Web of Science, Scopus, Global Health and Cab International; WHO Global Library; Psych INFO, CINAHL, AHMED, National Health Service (NHS) Evidence Health Information Resources, and Google Scholar. The following databases for international conference proceedings were also searched: Conference Proceedings Citation Index via Web of Knowledge and Zetoc via British Library. Reference lists of eligible articles were hand checked for additional citations. International experts in the field were contacted to ask for any relevant studies not captured through our database searches. We also searched the grey literature through Open Grey and The Grey Literature Report. Finally, the following registers were searched to locate ongoing studies: The Cochrane Central Register of Controlled Trials, International Standardized Randomized Control Trial Number Registry, WHO International Clinical Trials Registry Platform, ClinicalTrials.gov, Australian and New Zealand Clinic Trials Registry, and Current Controlled Trials. There was no language restriction. The search strategies were published in our systematic review protocol.[15]

Study selection

Records retrieved from the databases were exported to Endnote for study screening, de-duplication, and overall management of the retrieved records. Study titles and abstracts were independently screened by two reviewers (CF and BN); any discrepancies were resolved by discussion. The same process was employed for full-text screening. Multiple reports based on the same study were reported as one study. Where data or information was missing from any study, we contacted authors requesting additional information.

Data extraction and management

A standardized form was developed and used to extract relevant data from each study. The data extraction form was piloted and revised prior to use in the review and was published alongside the protocol for this study.[15] Data extraction was completed independently by two reviewers (CF and BN) and discrepancies were resolved by discussion.

Quality assessment

All included studies were assessed for quality and risk of bias by two independent reviewers (CF and BN) using the Effective Public Health Practice Project (EPHPP) tool (http://www.ephpp.ca/tools.html). In addition to a global rating for each study, the EPHPP tool provides individual ratings for six domains of study quality, including appropriateness of study design for the research question, selection bias, exposure assessment, outcome assessment, data analysis, and generalizability of findings. The two reviewers graded the quality of each study with regards to each of these domains. The quality grading derived from

each of the domains informed an overall grading for each study. For each study, the grading for the domains individually and the global study rating were assigned one of the three categories of risk of bias: weak, moderate, or strong. Concerning the domain on confounder adjustment, we considered the number and type of potential confounders adjusted in the studies, with close attention to the confounding factors listed in our own causal diagram (see Figure S1).

Analysis

We tabulated the features and key findings of the studies in order to provide a descriptive summary of the literature. We employed both narrative and quantitative synthesis of the underlying evidence. The quantitative synthesis (meta-analysis) was undertaken for studies judged to be reasonably homogenous with regards to similarity in the clinical, methodological, and statistical aspects. We used the random-effects meta-analysis approach for this purpose and included the adjusted risk estimates from each study. We included only cohort studies in the meta-analyses and not cross-sectional and case-control studies. Studies reporting odds ratios as effect measures were first converted to risk ratios before combining in meta-analyses with studies reporting risk ratios. Conversion of odds ratios to risk ratios was undertaken using the formulae by Grant, which given as follows: RR = OR/(1-p0+(p0 x OR)); where p0 is the baseline risk.[16] We quantified heterogeneity between studies using the I^2 test. We performed the following stratified analyses for each outcome: by type of stress indicator and timing (trimester) of exposure during pregnancy. To enhance comparability between studies that categorized any of the exposures as binary, we collapsed estimates from exposure categories in studies that used multiple exposure categories by using the Mantel-Haenszel approach,[17] thus in all analyses we estimated the risk of maternal stress versus no stress: we estimated the role of maternal exposure to any type of stress indicator (i.e. any of the studied stressors – anxiety, depression, bereavement, work-related stress, or NLEs), specific stress indicators, and trimester of exposure in relation to the outcomes. We used funnel plots to evaluate the potential for publication bias and small study effects and calculated the Begg and Egger's test for this purpose.[18] Meta-analysis was undertaken using Stata 14 statistical software.

RESULTS

In total, we identified 9779 articles, of which 7110 were included for screening by title and/or abstract after de-duplication. Of these, 7001 were excluded for not meeting the inclusion criteria and 109 articles were assessed for full text screening. A further 77 articles were excluded, leaving 32 articles (based on 30 studies) that met our inclusion criteria for narrative

synthesis; 24 papers (based on 22 studies) were included in at least one meta-analysis (Figure 1).[19-50]

Study characteristics

The key characteristics of the studies are presented in Table E1. No experimental studies were found; therefore only analytical epidemiological studies were included, which comprised of 27 cohort studies, two case-control studies, and one cross-sectional study. The type of psychosocial stress indicators investigated in the studies included anxiety,[21-24,27,30,35,36,48,49] depression,[22-24,30,35,37,41,42] bereavemet,[29,32,38] work-related stress,[33,36,47,48] and NLEs,[19,20,25,26,28,31,34,39,40,43-46,49,50] which were usually comprised of a composite of different indicators of stressors. Most studies assessed maternal stress using self-completed validated questionnaire; in a few studies maternal stress was assessed from population registers, particularly stress resulting from bereavement of a family member. Twelve studies assessed the impact of maternal stress on asthma,[20,27-32,34,37,38,42,46] eight studies on atopic eczema/dermatitis,[22-24,28,31,44,47,48] ten studies on wheeze,[20,24-28,30,35,42,43,46] three studies on allergic rhinitis,[24,28,31] three on atopic sensitization,[27,31,42] and six studies on cord blood IgE or cytokines[19,21,36,39,45,50] (Table S1).

Risk of bias within studies

Table S2 provides details of the quality grading for the studies. Of the 30 studies graded for quality, four were strong, 25 were moderate, and one study was weak. Whilst all studies scored moderate or strong on exposure and outcome assessment, only one study scored weak on study design as it was based on a cross-sectional data. Six studies were graded weak for selection bias, whereas two studies were graded weak for confounding adjustment; no study was graded strong for selection bias and confounding adjustment.

Prenatal stress and offspring asthma

Prenatal maternal exposure to any type of stress indicator was associated with an increased risk of asthma onset (hazard ratio (HR) 1.13, 95%CI 0.98-1.32; I^2=91.5%) and current or ever asthma (RR 1.13, 95%CI 1.03-1.24; I^2=83.5%) in the offspring, although result for asthma onset was not statistically significant (Figure 2, Panel A). Concerning the type of stress indicators, only anxiety was significantly associated with an increased risk of asthma (RR 1.28, 95%CI 1.16-1.41; I^2=0%) (Figure 2, Panel B). Concerning the timing of prenatal maternal stress, only exposure during the third trimester was significantly associated with an increased risk of asthma (OR 1.45, 95%CI 1.08-1.94; I^2=78%) for the studies that measured current and ever asthma (Figure 3, Panel B). Bereavement of the death of a child (HR 1.28,

95%CI 1.10-1.48; I^2=0%) or of a spouse (HR 1.40, 95%CI 1.03-1.90; I^2=1.3%), but not of a parent or sibling, increased the risk of asthma onset in the offspring (Figure 4).

Prenatal stress and offspring atopic eczema/dermatitis

Prenatal maternal exposure to anxiety (RR1.29, 95%CI 0.95-1.76; I^2=29.2%), depression (RR 1.45, 95%CI 1.12-1.89; I^2=0%), NLEs (OR 1.18, 95%CI 0.92-1.51; I^2=0%), and work stress (OR 1.32, 95%CI 1.16-1.50) was associated with increased risk of atopic eczema/dermatitis in the offspring, but only depression and work stress were statistically significant (Figure 5, Panel A). Maternal exposure to stress during the third and any trimester, but not during the second trimester, increased the risk of offspring atopic eczema/dermatitis (Figure 5, Panel B).

Prenatal stress and offspring wheeze

Prenatal maternal exposure to anxiety (RR 1.19, 95%CI 1.01-1.39; I^2=52%), depression (OR 1.74, 95%CI 1.42-2.13; I^2=0%), and NLEs (RR 1.23, 95%CI 1.00-1.52; I^2=88.3%) (Figure 6, Panel A) was associated with an increased risk of wheeze in the offspring. The increased risk was greater for maternal exposure to stress during the second and third than any trimester (Figure 6, Panel B). When we investigated the impact on different wheezing phenotypes, maternal stress increased the risk of early-onset, late-onset, and persistent wheeze, although the impact on late-onset wheeze was not statistically significant (Figure 7).

Prenatal stress and offspring allergic rhinitis

Prenatal maternal exposure to any type of stress indicator was associated with an increased risk of subsequent allergic rhinitis in the offspring (OR 1.36, 95%CI 1.08-1.71; I^2=43.7%) (Figure S2). These results were similar when the study by Hartwig et al was analyzed separately for allergic rhinitis at six and 14 years.[31]

Prenatal stress and offspring atopic sensitization

Prenatal maternal exposure to any stress indicator was associated with a decreased risk of atopic sensitization in the offspring (OR 0.92, 95%CI 0.86-0.98; I^2=0%) (Figure 8). These results were similar when the study by Hartwig et al was analyzed separately for atopic sensitization at six and 14 years.[31] The measurement and definition of atopic sensitization differed between the studies: whilst Cookson[27] defined it as ≥2 mm weal skin prick test to aeroallergens, Hartwig[31] and Reyes[42] were based on IgE measurements of a combination of both food and inhalant allergens.

Prenatal stress and cord blood IgE and cytokines

Studies reporting the impact of maternal prenatal stress on cord blood IgE and cytokines were heterogeneous, particularly with regards to the type of outcomes investigated, hence a meta-analysis was not undertaken to pool the results of these studies together. However, across studies, maternal exposure to stress during pregnancy was associated with raised cord blood specific and total IgE.[36,39,45,50] One study reported an alteration of cord blood cytokine profiles (IL-12, IL-1β, IL-4, IL-5, IL6, IL-8, and TNF-α) in offspring of mothers exposed to stress during pregnancy.[19]

Assessment of publication bias

Figure S3 shows the funnel plot evaluating possible publication bias and small study effect: by interpretation, a symmetric funnel plot indicates less likelihood of publication bias influencing the estimates of effect. Indeed, the funnel plot in Figure S3 is modestly symmetric. The associated p-values for Egger's test (where Egger's test of with $P<0.05$ indicating presence of publication bias) were as follows: atopic eczema/dermatitis studies $p=0.949$; atopic sensitization studies $p=0.855$; wheeze studies $p<0.001$; asthma studies $p=0.828$; and allergic rhinitis studies $p=0.493$.

DISCUSSION

This study provides the most comprehensive and robust synthesis of the evidence to date on the association between prenatal maternal exposure to psychosocial stress and the risk of allergy and asthma in the offspring. The majority of included studies were at moderate risk of bias. Overall, prenatal maternal exposure to any psychosocial stress was associated, albeit modestly, with an increased risk of asthma, atopic eczema/dermatitis, wheeze and its phenotypes, and allergic rhinitis. A decreased risk was seen for atopic sensitization. Although these results were similar for specific indicators of stress, exposure to anxiety and depression had the strongest effects. The third trimester appeared to be more vulnerable period of exposure compared to first and second trimesters. Specific to asthma, maternal bereavement of a child or a spouse, but not of a parent or sibling, increased the risk of asthma in the offspring.

We undertook an exhaustive search of the literature, covering the major medical and public health databases, which was supplemented through search of grey literature and through contacting experts in the field. The search strategies were implemented and published in order to enhance reproducibility. It is therefore unlikely that we missed any relevant literature, this being confirmed by somewhat symmetric funnel plot on publication bias and small study effect. Two reviewers independently performed each stage of the review, including literature screening, data extraction, and quality appraisal of included studies. We developed,

published and registered a detailed protocol[15] prior to undertaking the review, which enhanced the transparency of the review process.

At the same time of publishing our review protocol, two related systematic reviews were published.[13,14] By the time we were planning the current review, no protocol was published for those reviews, neither were they registered in PROSPERO; hence our preliminary search did not identify them. Nevertheless, in the first review only asthma and wheeze were outcomes, which limits its scope.[13] The second review considered all possible asthma and allergic outcomes, but only provided narrative synthesis of the existing literature.[14] We aimed for a comprehensive and exhaustive approach by including the full spectrum of allergy and asthma outcomes and considering whether the type of stressor and trimester of exposure were important. We identified 30 unique studies as against 16 studies in the second review[14] and 18 studies as against 10 studies in the first review with regards to asthma/wheeze outcomes.[13] Whilst the second study[14] performed only narrative synthesis, with careful consideration, we judged several of these studies to be reasonably homogenous to be combined in meta-analyses with respect to exposure and outcome definitions, study design, and statistical analyses. Regardless of the differences in methodological rigor and comprehensiveness, the conclusions from the two previous systematic reviews align with our findings, indicating that prenatal maternal exposure to psychosocial stress was associated with increased risk of asthma and allergic disease in the offspring.

The majority of studies included in our review were graded as at moderate risk of bias, with only four being graded as strong studies, an indication of the potential for biases across studies, particularly within the domains of selection bias and confounding adjustment. In particular, most studies assessed maternal prenatal stress using self-report questionnaires, usually for recall of previous exposure to stress across several months. No study used both self-report and objective measures at regular intervals, which would provide a more robust and informative understanding of unique and combined contribution of environmental and mechanistic factors involved in the developmental pathway of atopic conditions. Several studies also assessed allergy outcomes using maternal subjective questionnaires and the age of onset of the outcomes was not consistent across all studies. Objective assessment of both maternal prenatal stress and offspring outcomes and within the same time-point will improve the underlying evidence and provide a stronger basis to evaluate whether these findings are causal.[14] The test for heterogeneity was significant for a number of associations, an indication of the variations in methods and measures between studies; however as we did not have sufficient number of studies for each of these associations, we were unable to further investigate the possible reasons for these significant heterogeneity tests.

Furthermore, as it was not feasible to perform a formal test between subgroups, it is possible that the associations found within subgroups may be a result of chance.

Although some studies have examined the role of maternal stress during the postpartum period and the child's exposure during infancy on subsequent risk of allergy and asthma in the child,[26,51] *a priori*,[15] the underpinning objective of our review was to assess the impact of prenatal stress on offspring's asthma and allergy. This objective aligns within the framework of the fetal programming hypothesis. Within this framework, we assumed that the pathway of prenatal stress influencing offspring asthma and allergy risk may be independent of the effects of postnatal and early life stress, hence we excluded all studies not investigating maternal prenatal stress. However, we cannot rule out the possibility that these findings may also be partly explained by postnatal or early life stress exposures.[52] Furthermore, whilst the timing of exposure was based on the trimester of assessment of prenatal stress, this single time-point assessment may fail to reflect specific trimester effect, as stressful events may be acute or may chronologically be present throughout pregnancy or may even be an extension of stressful events prior to pregnancy.[52]

Regardless of the type of stress indicator, timing of exposure, and the type of allergy and asthma outcomes, by bringing together all the available evidence, the current evidence synthesis shows that prenatal maternal psychosocial stress is associated with an increased, albeit modest, risk of asthma and allergy in the offspring. The findings were particularly more evident for depression and anxiety than for other indicators of prenatal stress. This could reflect that anxiety and depression scores were based on self-assessment and questionnaires. However, it should also be noted that the largest study had a strongly positive result.[32] This study also had a strong design due to using a 'natural experiment' design and an objective measure of hospitalized asthma, thereby avoiding the risks of reporting bias and reverse causation.[32] In addition, although depression and anxiety reflect mood states, they are robust correlates of psychosocial stress and strongly predispose to stress-related conditions, such as smoking, poor diet, poor sleeping habits, and poor quality of life which may also lead to asthma and allergy in offspring.[53]

Whilst our observations may represent causal relationships, they may also be a consequence of over-reporting of offspring disease status by distressed mothers[22,54]or due to residual confounding in the original studies. The number and type of confounders adjusted varied across included studies. In particular, the omission of key confounders in several studies, including maternal allergic history, pregnancy complications, acid reflux conditions, medication use during pregnancy (e.g. antibiotics and acetaminophen), and pregnancy

weight gain indicates sub-optimal confounding adjustment and therefore may impact on the observed risk. One way to test for residual confounding in fetal programming studies is to use family design studies such as sibling studies[54,55] or to use a paternal negative control. A positive association for paternal exposure to stress during the mother's pregnancy and subsequent offspring asthma or allergy may indicate residual confounding is affecting the prenatal maternal stress and offspring asthma association. A recent study using fathers as a negative control in this way, found that after adjusting for measured confounders there was no evidence for residual confounding.[56]

One hypothesized pathway through which stress may influence risk of asthma and allergy is that high levels of cortisol resulting from external stress may potentiate cell differentiation from Th1 to Th2 phenotype.[12] Prenatal stress-generated cortisol has been linked to increased airway responsiveness in the offspring in animal models.[12] This indicates that prenatal maternal stress may increase risk of atopic sensitization in the offspring and subsequent allergic disease and asthma. However, our findings did not support this line of reasoning, but showed a decreased risk of atopic sensitization and increased risk of clinical allergic outcomes and asthma. The reason for these differential findings between atopic sensitization and other clinical outcomes is unclear. Other suggested mechanism indicate that prenatal maternal stress may cause epigenetic effects with deoxyribonucleic acid (DNA) methylation and altered gene expression in the placenta,[57] but this proposal and its implication for the development of allergy and asthma in the offspring has yet to be determined.[51] There is some evidence that prenatal stress exposure can influence the composition of the offspring's intestinal microbiota and may also result in increased susceptibility to asthma.[58,59]

CONCLUSION

Prenatal maternal psychosocial stress – particularly anxiety and depression - was associated with a modest increased risk of asthma and allergy in the offspring. Whilst exposure during the third trimester had the greatest impact compared to the first and second trimesters, this may represent cumulative stress exposure throughout pregnancy rather than a trimester-specific effect. These findings may represent a causal association; they may also result from inherent biases in the included studies, particularly residual confounding. Further studies with objective measures of prenatal stress and optimal adjustment of confounding are required, as well as studies elucidating the likely mechanisms for these associations.

CONFLICTS OF INTEREST

The authors declare no competing interest related to this work.

AUTHORS' CONTRIBUTIONS

BN conceived the idea for this work. It was drafted by CF and BN and was then revised after several rounds of critical comments from AS, ADG, BKB, and CA.

FUNDING

This work received no specific funding. BN was supported by the Institute for Advanced Social Research Fellowship, University of Tampere, Finland; School of Health Sciences, University of Tampere, Finland; and Farr Institute and Asthma UK Centre for Applied Research, University of Edinburgh. BN acknowledges the support of the Knut and Alice Wallenberg Foundation and the Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg. This work was part of CF dissertation for the award of MPH degree at The University of Edinburgh. CF's Master course was in part supported by Student Awards Agency for Scotland (SAAS). CA acknowledges support from the Swedish Research Council through the ***S***wedish ***I***nitiative for Research on ***M***icrodata in the ***S***ocial ***a***nd ***M***edical Sciences (SIMSAM) framework grant no. 340-2013-5867. BKB was supported by FORTE and the commission under a COFAS Marie Curie Fellowship (grant no 2015-01208).

ACKNOWLEDGEMENT

We are grateful to Marshall Dozier and Angela Nicholson, the Academic Librarians at The University of Edinburgh, for their advice on the construction of search strategies. Finally, we wish to express our sincere gratitude to the experts contacted who responded.

REFERENCES

1. Henderson AJ, Warner JO. Fetal origins of asthma. *Semin Fetal Neonatal Med* 2012; 17: 82-91.
2. Tedner SG, Örtqvist AK, Almqvist C. Fetal growth and risk of childhood asthma and allergic disease. *Clin Exp Allergy* 2012; 42: 1430-1447.
3. Ortqvist AK, Lundholm C, Calrström E, Lichtenstein P, Cnathingius S, Almqvist C. . Familial factors do not confound the association between birth weight and childhood asthma *Pediatrics* 2009; 124: e737-e743.
4. Holt PG, Jones CA. The development of the immune system during pregnancy and early life. *Allergy* 2000; 55: 688-697.
5. Talge NM, Neal C, Glover V. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? *J. Child Psychol Psychiatry* 2007; 48: 245–261.
6. Mulder EJH, Robles de Medina PG, Huizink AC, Van den Bergh BR, Buitelaar JK, Visser GH. Prenatal maternal stress: effects on pregnancy and the (unborn) child. *Early Hum Dev* 2002; 70: 3–14.
7. Holt PG. Key factors in the development of asthma: atopy. *Am J Respir Crit Care Med* 2000; 161: 172–175.
8. Merlot E, Couret D, Otten W. Prenatal stress, fetal imprinting and immunity. *Brain Behav Immun* 2008; 22: 42-51.
9. Spiers JG, Chen HJ, Sernia C, Lavidis NA. Activation of the hypothalamic-pituitary-adrenal stress axis induces cellular oxidative stress. *Front Neurosci* 2015; 8: 456.
10. Reynolds, R. M., Labad, J., Buss, C., Ghaemmaghami, P. & Räikkönen, K. Transmitting biological effects of stress in utero: implications for mother and offspring. *Psychoneuroendocrinology* 2013; 38: 1843–1849.
11. Weinstock M. The potential influence of maternal stress hormones on development and mental health of the offspring. *Brain Behav Immun* 2005; 19: 296–308
12. Von Hertzen, L. C. Maternal stress and T-cell differentiation of the developing immune system: Possible implications for the development of asthma and atopy. *J. Allergy Clin. Immunol* 2002; 109: 923–928.

13. van de Loo KF, van Gelder MM, Roukema J, Roeleveld N, Merkus PJ, Verhaak CM. Prenatal maternal psychological stress and childhood asthma and wheezing: a meta-analysis. *Eur Respir J* 2016; 47: 133-146.
14. Andersson NW, Hansen MV, Larsen AD, Hougaard KS, Kolstad HA, Schlunssen V. Prenatal maternal stress and atopic diseases in the child: a systematic review of observational human studies. *Allergy* 2016; 71: 15-26.
15. Flanigan C, Sheikh A, Nwaru BI. Prenatal maternal psychosocial stress and risk of asthma and allergy in their offspring: protocol for a systematic review and meta-analysis. *NPJ Prim Care Respir Med* 2016; 26: 16021.
16. Grant R.L. Converting an odds ratio to a range of plausible relative risks for better communication of research findings. *BMJ* 2014; 348: g2124
17. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959. 22: 719-48.
18. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 1088-101.
19. Andersson NW, Li Q, Mills CW, Ly J, Nomura Y, Chen J. Influence of prenatal maternal stress on umbilical cord blood cytokine levels. *Arch Womens Ment Health* 2016; 19: 761-767.
20. Bandoli G, von Ehrenstein O, Ghosh JKC, Flores MES, Schetter CD, Ritz B. Prenatal maternal stress and the risk of lifetime wheeze in young offspring: an examination by stressor and maternal ethnicity. *J Immigrant Minority Health* 2016; 18: 987-995.
21. Bidaki R, Karimi M, Mojibyan M, Nodoshan HH, Zare A, Rafiee P, et al. Maternal stress in pregnancy based on Holmes-Rahe questionnaire and umbilical cord IgE. *Can J Med* 2011; 2: 76-86.
22. Braig S, Weiss JM, Stalder T, Kirschbaum C, Rottenbacher D, Genuneit J. Maternal prenatal stress and child atopic dermatitis up to age 2 years: The Ulm SPATZ health study. *Pediatr Allergy Immunol* 2017; 28: 144-151.
23. Chang HY, Suh DI, Yang SI, Kang MJ, Lee SY, Lee E, et al. Prenatal maternal distress affects atopic dermatitis in offspring mediated by oxidative stress. *J Allergy Clin Immunol* 2016; 138: 468-475.
24. Cheng TS, Chen H, Lee T, Teoh OH, Shek LP, Lee BW, et al. An independent association of prenatal depression with wheezing and anxiety with rhinitis in infancy. *Pediatr Allergy Immunol* 2015; 26: 765-771.
25. Chiu YHM, Coull BA, Sternthal MJ, Kloog I, Schwartz J, Cohen S, et al. Effects of prenatal community violence and ambient air pollution on childhood wheeze in an urban population. *J Allergy Clin Immunol* 2014; 133: 713-722

26. Chiu YHM, Coull BA, Cohen S, Wooley A, Wright RJ. Prenatal and postnatal maternal stress and wheeze in urban children: Effect of maternal sensitization. *Am j Respir Crit Care Med* 2012; 15: 147-154.
27. Cookson H, Granell R, Joinson C, Ben-Shlomo Y, Henderson AJ. Mothers' anxiety during pregnancy is associated with asthma in their children. *J Allergy Clin Immunol* 2009; 123: 847-853.
28. de Marco R, Pesce G, Girardi P, Marchetti, P, Rava M, Ricci P, et al. Foetal exposure to maternal stressful events increases the risk of having asthma and atopic diseases in childhood. *Pediatr Allergy Immunol* 2012; 23: 724-729.
29. Fang F, Hoglund CO, Arck P, Lundholm C, Langstrom N, Lichtenstein P, et al. Maternal bereavement and childhood asthma-analyses in two large samples of Swedish children. *PLoS One* 2011; 6: e27202.
30. Guxens M, Sonnenschein-van der Voort AM, Tiemeier H, Hofman A, Sunyer J, de Jongste JC, et al. Parental psychological distress during pregnancy and wheezing in preschool children: the Generation R Study. *J Allergy Clin Immunol* 2014; 133: 59-67.
31. Hartwig IR, Sly PD, Schmidt LA, van Lieshout RJ, Bienenstock, J, Holt PG, et al.. Prenatal adverse life events increase the risk for atopic diseases in children, which is enhanced in the absence of a maternal atopic predisposition. *J Allergy Clin Immunol* 2014; 134: 160-169.
32. Khashan AS, Wicks S, Dalman C, Henriksen TB, Li J, Mortensen PB, et al. Prenatal stress and risk of asthma hospitalization in the offspring: a Swedish population-based study. *Psychosom Med* 2012; 74: 635-641.
33. Larsen AD, Schlunssen V, Christensen BH, Bonde JP, Obel C, Thulstrup AM, et al. Exposure to psychosocial job strain during pregnancy and odds of asthma and atopic dermatitis among 7-year old children - a prospective cohort study. *Scand J Work Environ Health* 2014; 40: 639-648.
34. Lee A, Chiu YHM, Rosa J, Jara C, Wright RO, Coull BA, et al. Prenatal and postnatal stress and asthma in children: Temporal- and sex-specific associations. *J Allergy Clin Immunol* 2016; 138: 740-747.
35. Lefevre F, Moreau D, Semon E, Kalaboka S, Annesi-Maesano I, Just J. Maternal depression related to infant's wheezing. *Pediatr Allergy Immunol* 2011; 22: 608-613.
36. Lin YC, Wen HJ, Lee YL, Guo YL. Are maternal psychosocial factors associated with cord immunoglobulin E in addition to family atopic history and mother immunoglobulin E? *Clin Exp Allergy* 2004; 34: 548-554.
37. Liu X, Olsen J, Pedersen LH, Agerbo E, Yuan W, Li J. Antidepressant use during pregnancy and asthma in the offspring. *Pediatrics* 2015; 135: e911-917.

38. Liu X, Olsen J, Agerbo E, Yuan W, Sigsgaard T, Li J. Prenatal stress and childhood asthma in the offspring: role of age at onset. *Eur J Public Health* 2015; 25: 1042-1046.
39. Peters JL, Cohen S, Staudenmayer J, Hosen J, Platts-Mills T A, Wright RJ. Prenatal negative life events increases cord blood IgE: interactions with dust mite allergen and maternal atopy. *Allergy* 2012; 67: 545-551.
40. Polloni L, Ferruzza E, Ronconi L, Lazzarotto F, Toniolo A, Bonaguro R et al. Perinatal stress and food allergy: a preliminary study on maternal reports. *Psychol Health Med* 2015; 20: 732-741.
41. Radkhakrishnan DK, Shariff S, Richard L, To T. Does maternal stress influence the development of asthma in childhood? *American Thoracic Society Conference 2016*; A63. Pediatric Asthma: Predictors and Outcomes; Thematic Poster Session, Sunday, May 15, 2016.
42. Reyes M, Perzanowski MS, Whyatt RM, Kelvin EA, Rundle AG, Diaz DM, et al.. Relationship between maternal demoralization, wheeze, and immunoglobulin E among inner-city children. Ann Allergy Asthma Immunol 2011; 107: 42-49.e41.
43. Rosa MJ, Just AC, Tamayo Y Ortiz M, Schnaas L, Svensson K, Wright RO, et al. Prenatal and postnatal stress and wheeze in Mexican children: sex-specific differences. *Ann Allergy Asthma Immunol* 2016; 116: 306-312.
44. Sausenthaler S, Rzehak P, Chen CM, Arck P, Bockelbrink A, Schaefer T, et al. Stress-Related Maternal Factors During Pregnancy in Relation to Childhood Eczema: Results From the LISA Study. *J Investig Allergol Clin Immunol* 2009; 19: 481-487.
45. Sternthal MJ, Enlow MB, Cohen S, Canner MJ, Staudenmayer J, Tsang K, et al.. Maternal interpersonal trauma and cord blood IgE levels in an inner-city cohort: A life-course perspective. *J Allergy Clin Immunol* 2009; 124: 954-960.
46. Turcotte-Tremblay AM, Lim R, Laplante DP, Kobzik L, Brunet A, King S. Prenatal maternal stress predicts childhood asthma in girls: project ice storm. *BioMed Res Int* 2014; 201717.
47. Wang IJ, Wen HJ, Chiang TL, Lin SJ, Chen PC, Guo YL. Maternal employment and atopic dermatitis in children: a prospective cohort study. *Br J Dermatol* 2013; 168: 794-801.
48. Wen HJ, Chiang TL, Lin SJ, Guo YL. Predicting risk for childhood asthma by pre-pregnancy, perinatal, and postnatal factors. *Pediatr Allergy Immunol* 2015; 26: 272-279.
49. Wood RA, Bloomberg GR, Kattan M, Conroy K, Sandel MT, Dresen A, et al.. Relationships among environmental exposures, cord blood cytokine responses,

allergy, and wheeze at 1 year of age in an inner-city birth cohort (Urban Environment and Childhood Asthma study). *J Allergy Clin Immunol* 2011; 127: 913-919.

50. Wright RJ, Visness CM, Calatroni A, Grayson MH, Gold DR, Sandel MT, et al.. Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. *Am J Respir Crit Care Med* 2010; 182: 25-33.
51. Kozyrskyi AL, Mai XM, McGrath P, Hayglass KT, Becker AB, Macneil B. Continued exposure to maternal distress in early life associated with an increased risk of childhood asthma. *Am J Respir Crit Care Med* 2008; 177: 142-147.
52. Brew BK, Lundholm C, Viktorin A, Lichtenstein P, Larsson H, Almqvist C. Longitudinal depression or anxiety in mothers and offspring asthma: a Swedish population-based study. *In J Epidemiol*. In press.
53. Beiter R, Nash R, McCrady M, Rhoades D, Linscomb M, Clarahan M, et al. The prevalence and correlates od depression, anxiety, and stress in a sample of college students. *J Affect Disord* 2015; 173: 90-96.
54. Havland I, Lundholm C, Lichtenstein P, Neidehiser J, Ganiban J, Spotts E, et al. The observed association between maternal anxiety and adolescent asthma: children of twin design suggest familial effects. *Plos ONE* 2013; 8: e66040.
55. Gong T, Brew BK, Sjolander A, Almqvist C. Towards non-conventional methods of designing register-based epidemiological studies: an application to pediatric research. *Scand J Pub Health* 2017; 45: 30-35.
56. Brew BK, Gong T, Williams DM, Larsson H, Almqvist C. Using fathers as a negative control exposure to test the Developmental Origins of Health and Disease Hypothesis: a case study on maternal distress and offspring asthma using Swedish register data. *Scand J Pub Health* 2017; 45: 36-40.
57. Trump S, Bieg M, Gu Z, Thürmann L, Bauer T, Bauer M, et al. Prenatal maternal stress and wheeze in children: novel insights into epigenetic regulation. *Sci Rep* 2016; 6: 28616.
58. Monk C, Spicer J, Champagne FA. Linking prenatal maternal adversity to developmental outcomes in infants: the role of epigenetic pathways. *Dev. Psychopathol* 2012; 24**:** 1361–1376.
59. Azad MB, Kozyrskyi AL Perinatal programming of asthma: The role of gut microbiota. *Clin Dev Immunol* 2012; 2012: 932072.

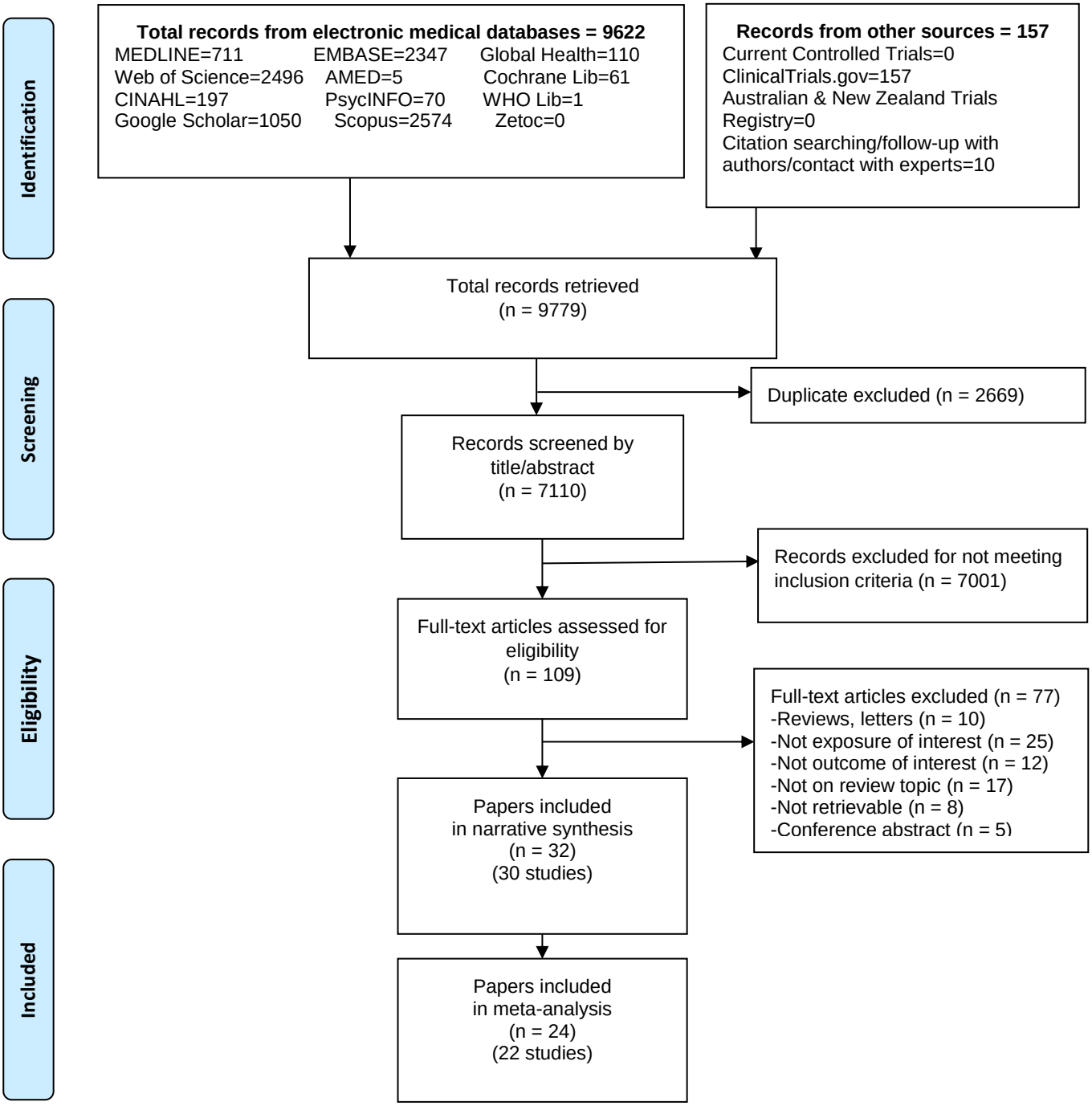
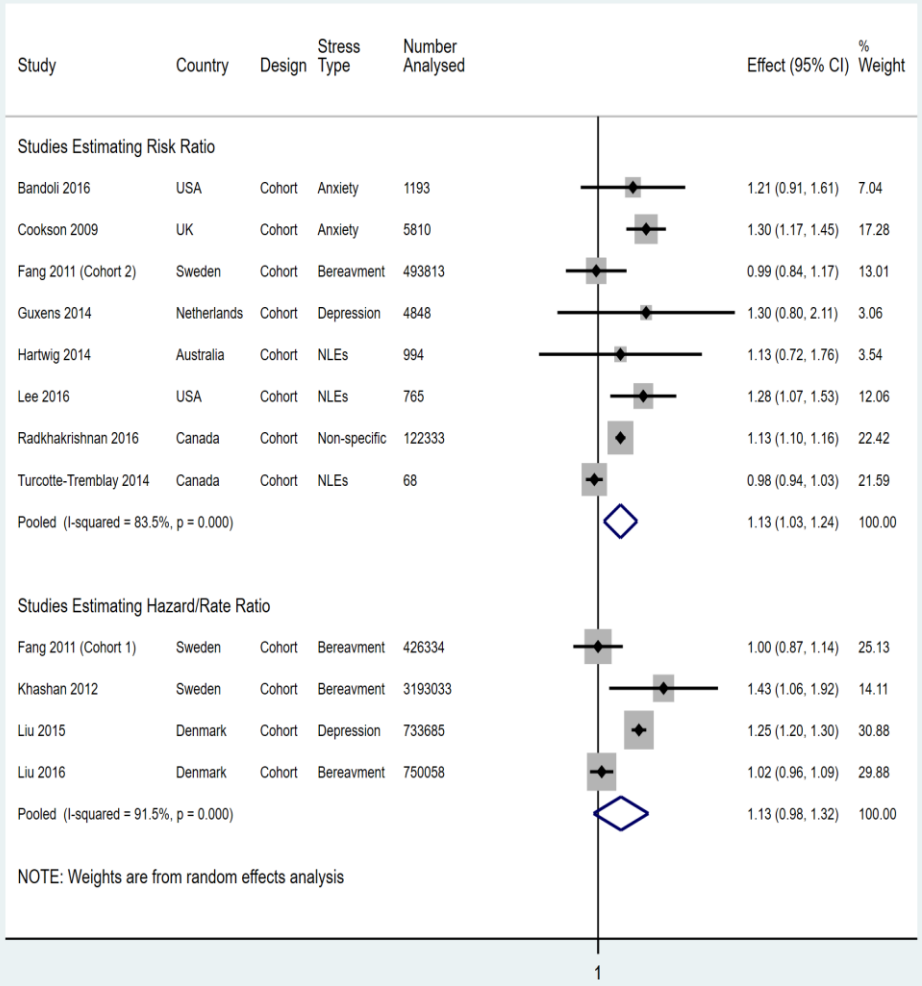


Figure 1. PRISMA flow diagram of studies on the association between maternal prenatal stress and risk of allergy and asthma in the offspring

PANEL A



PANEL B

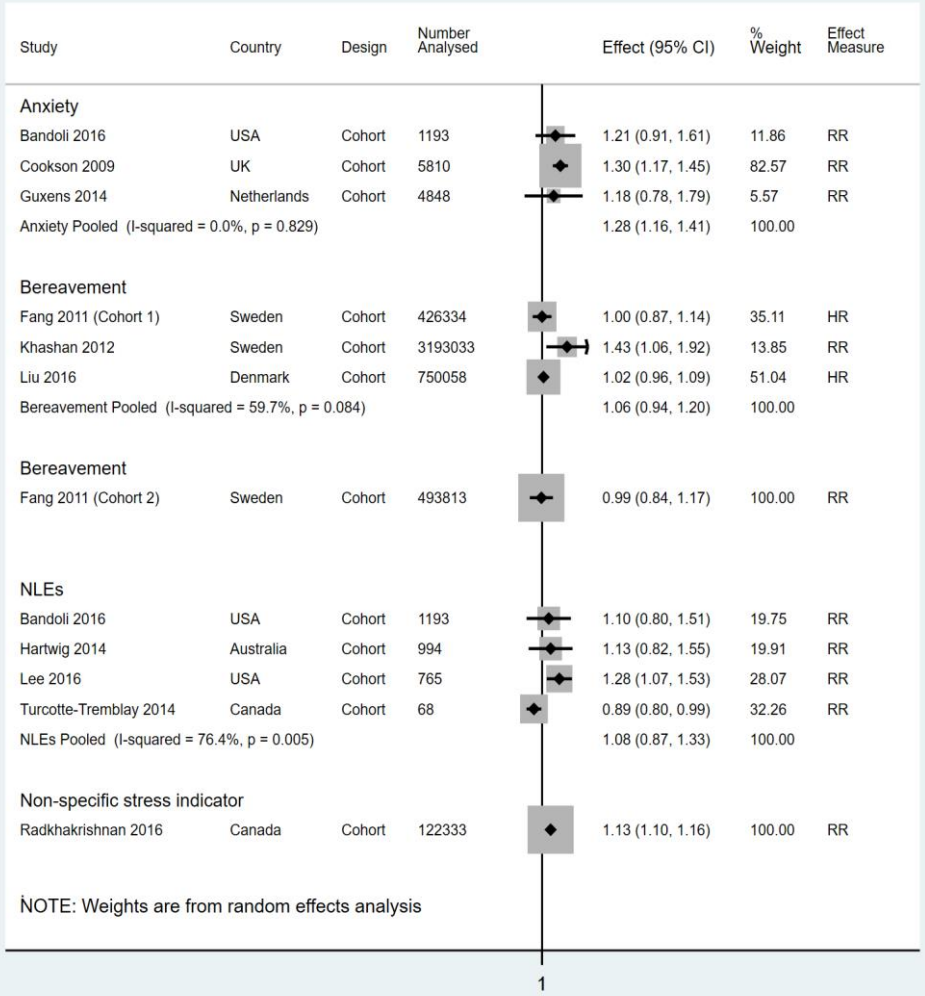
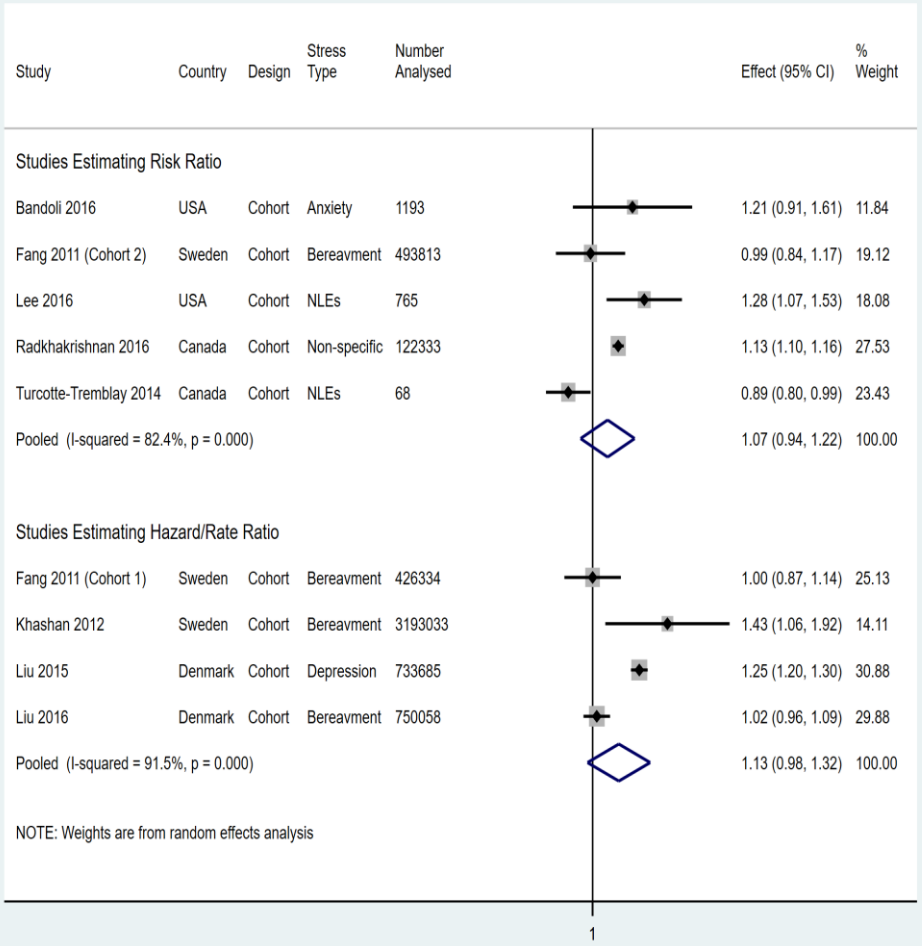


Figure 2. Association between prenatal maternal stress (**Panel A**: any type of stress and **Panel B** by type of stress) and risk of asthma in the offspring. NLEs = Negative life events. The results included Hartwig 2014 and Liu 2016 populations of 14 years and 4-15 years, respectively, as these were not substantially different from the population of 6 years and 0-3 years, respectively, also presented in the studies.

PANEL A



PANEL B

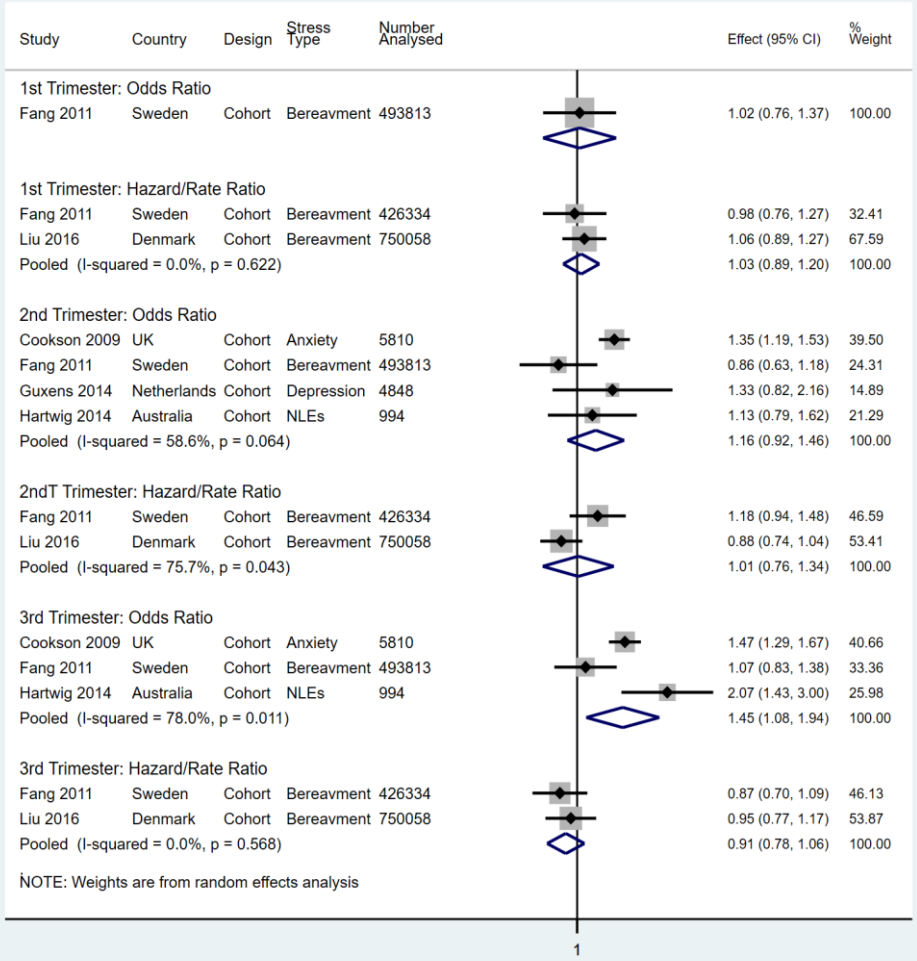


Figure 3. Association between prenatal maternal stress and risk of asthma in the offspring, by timing of exposure during pregnancy: **Panel A**: during any trimester; **Panel B**: at different trimesters. The results included Hartwig 2014 and Liu 2016 population of 14 years and 4-15 years as these were not substantially different from the population of 6 years and 0-3 years also presented in the studies.

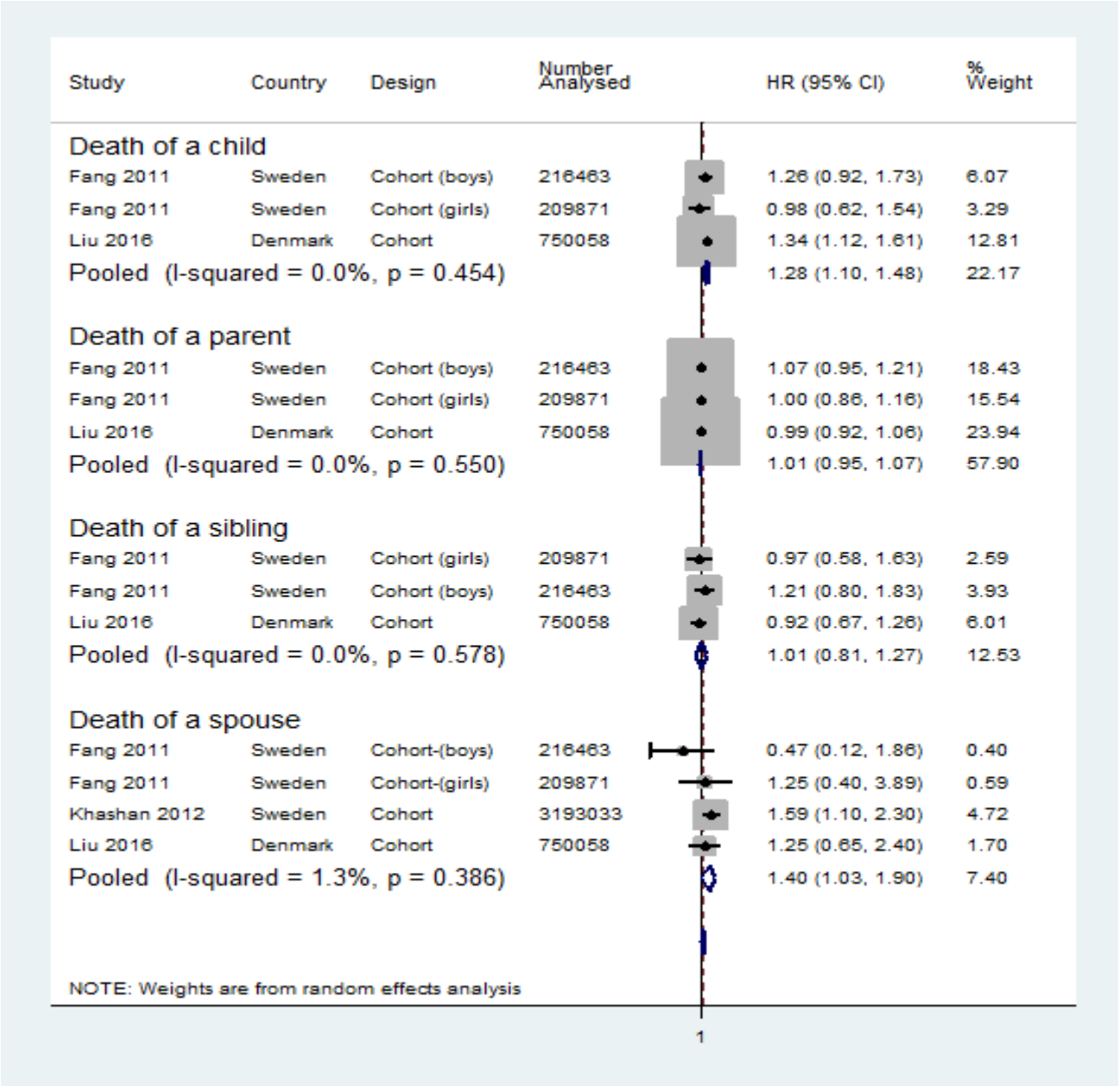
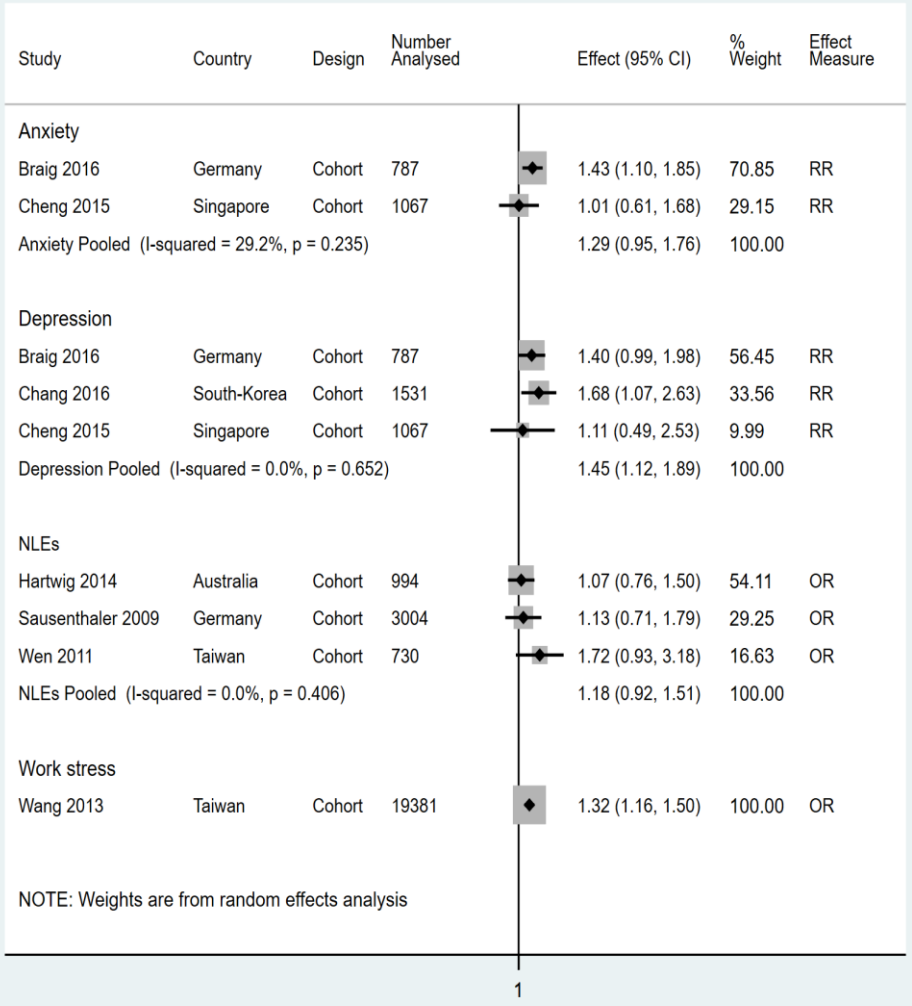


Figure 4. Association between maternal stress resulting from bereavement of a relative and risk of asthma in the offspring, by type relative. The results included Hartwig 2014 and Liu 2016 population of 14 years and 4-15 years as these were not substantially different from the population of 6 years and 0-3 years also presented in the studies.

PANEL A



PANEL B

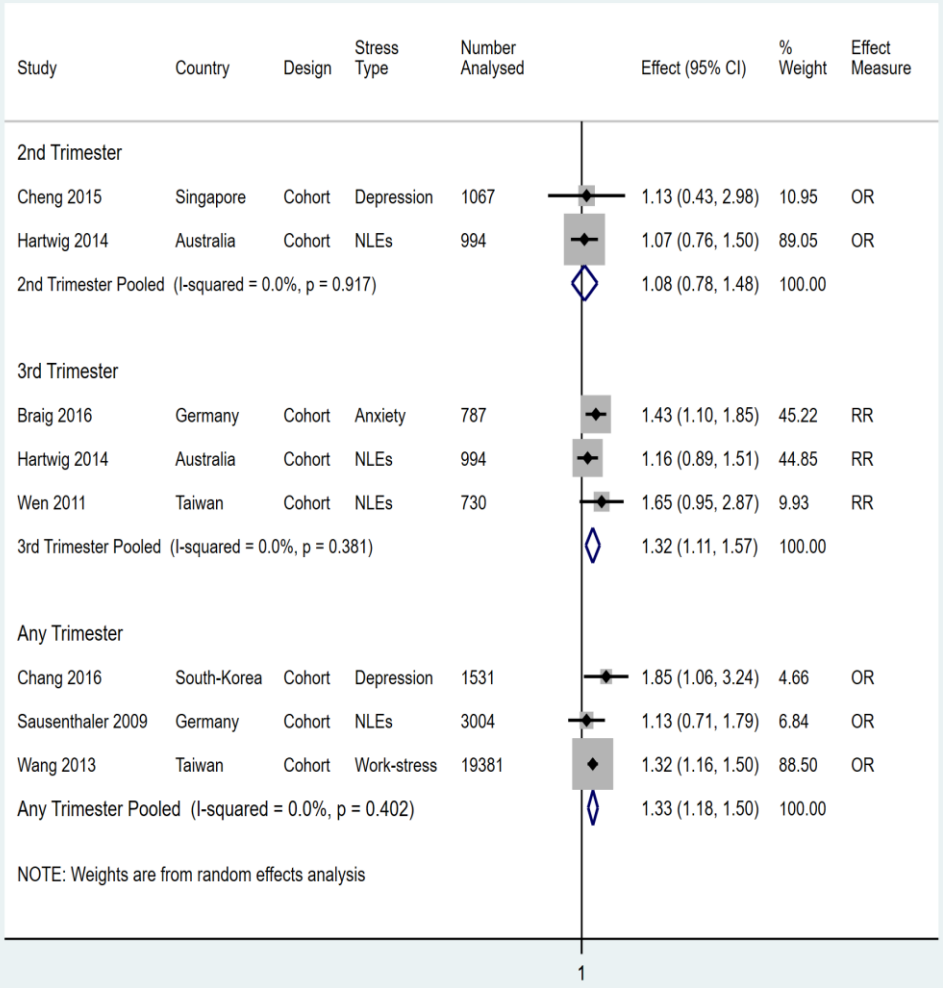
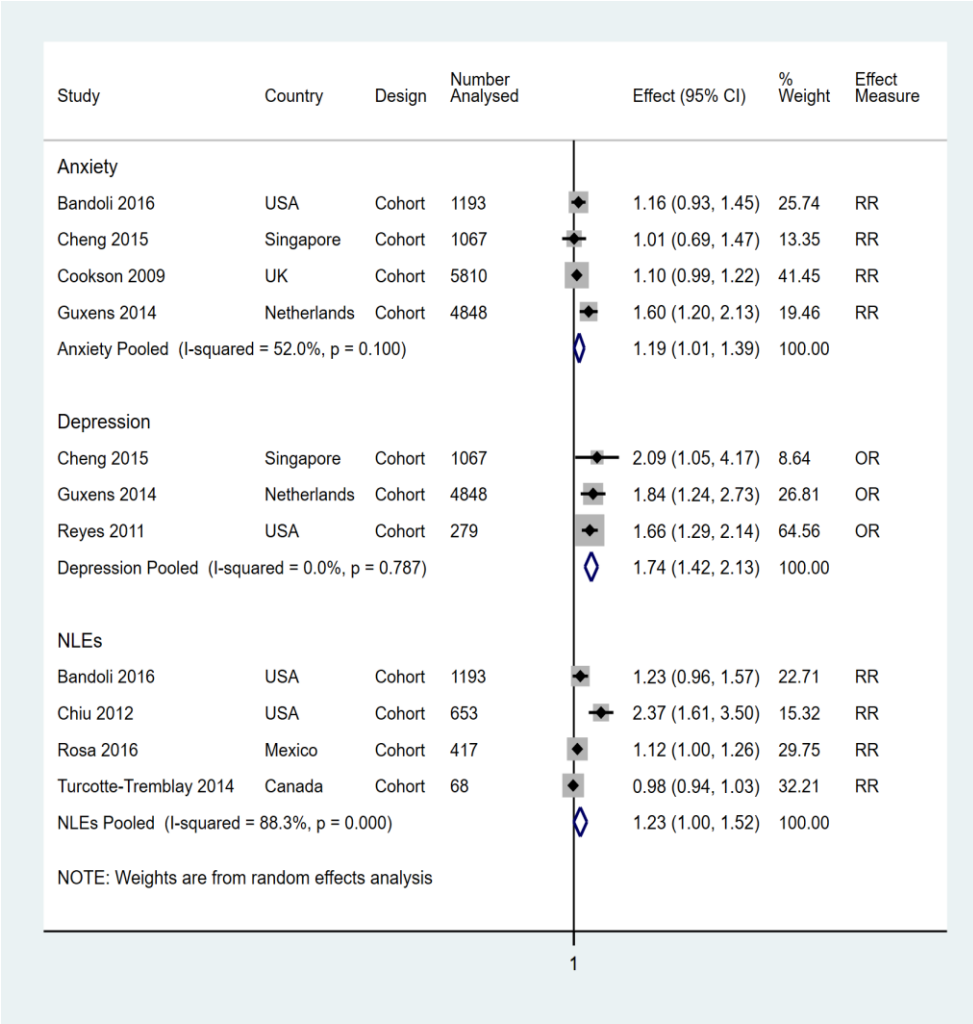


Figure 5. Association between maternal prenatal stress and risk of atopic eczema/dermatitis in the offspring, by type of stress (**Panel A**) and timing of exposure during pregnancy (**Panel B**). NLEs = negative live events. No major differences when Hartwig 2014's 6-year-olds and 14-year-olds were analysed separately, hence we presented the results for 6-year-olds

PANEL A



PANEL B

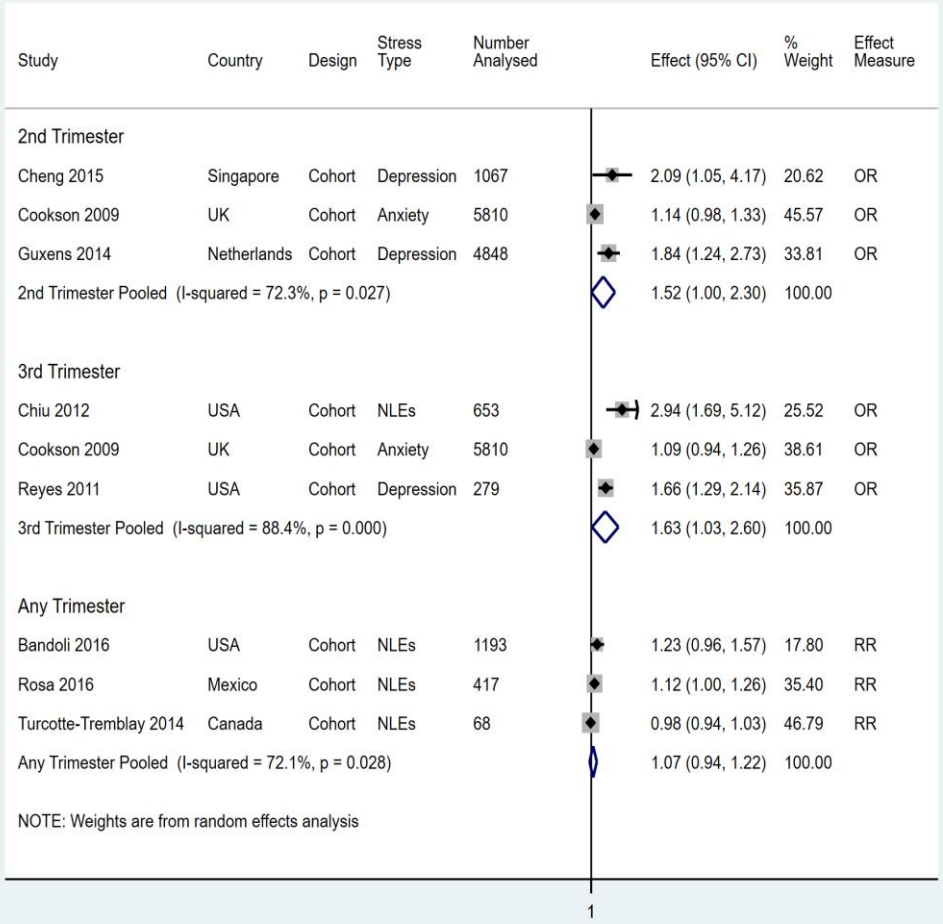


Figure 6. Association between maternal prenatal stress and risk of wheeze in the offspring, by type of stress (**Panel A**) and timing of exposure during pregnancy (**Panel B**). NLEs = negative live events. No major differences when Cookson 2009's wheeze at 6-18 months and 69-81 months were analysed separately, hence we present the results for the 6-18 month age group

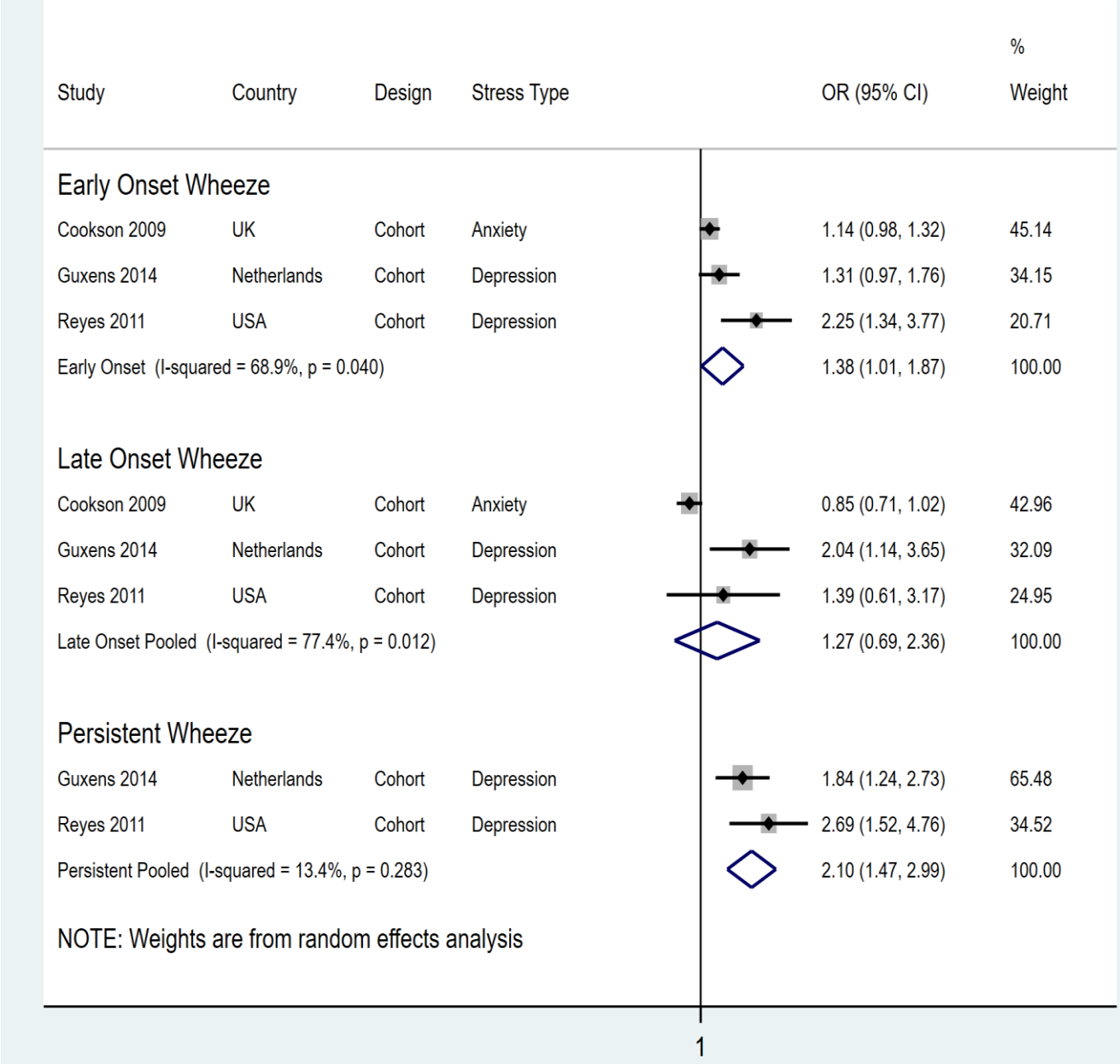


Figure 7. Association between maternal prenatal stress and risk of wheeze phenotypes in the offspring

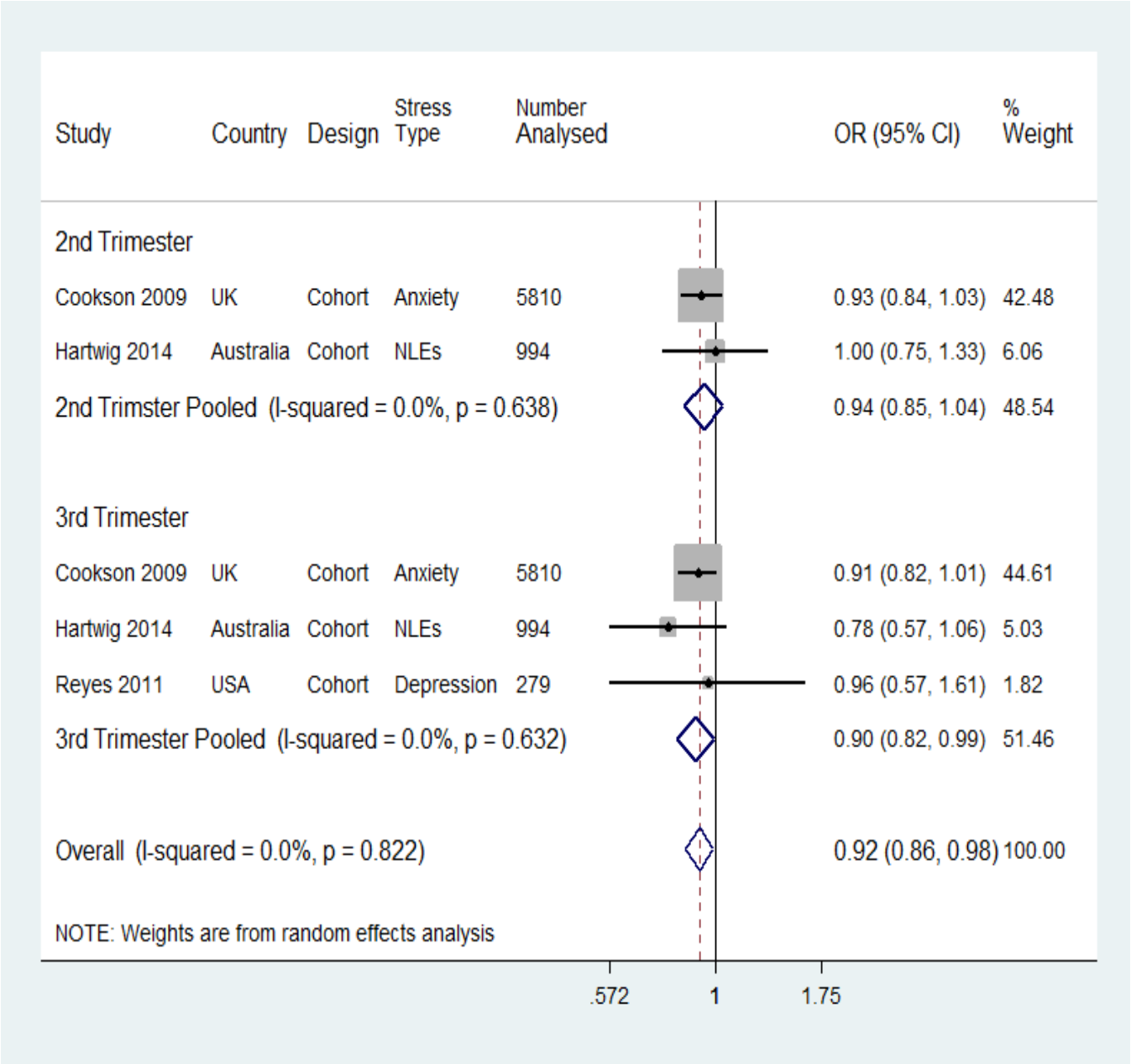


Figure 8. Association between maternal prenatal stress and atopic sensitisation in the offspring, by timing of exposure during pregnancy: No major differences when Hartwig 2014's 6-year-olds and 14-year-olds were analysed separately, hence we presented the results for 6-year-olds

Table S1: Main characteristics, key results, and overall risk of bias of studies on the association between maternal psychosocial stress during pregnancy and risk of allergy and asthma in the offspring

Reference, country; and study design	Study population *N* (maternal-child; source of study population)		Age of children/ follow-up years	Type of prenatal stress and assessment	Outcomes and assessment	Key results	Overall risk of bias assessment
	Number recruited	Number analysed					
Andersson et al 2016; USA; Prospective cohort study	50	43	At birth	Maternal reported anxiety and negative life events (NLEs) during the 2nd trimester using Self-reported using Perceived Stress Scale (PSS-14); State-Trait anxiety inventory (STAI); Life Experience Interview	Cord blood cytokines: IL-12, IL-1β, IL-4, IL-5, IL6, IL-8, and TNF-α	Prenatal maternal stress increased the risk of alteration of cord blood cytokine profiles in the offspring	Moderate
Bandoli et al 2016; USA; Prospective cohort study	6,347	1,193	2.3-5.8 years	Maternal reported anxiety, chronic stress, and NLEs (loss of car/job/home, serious arguments with partner, close acquaintance with health, drug or legal problems, death of a relative, threatened with physical harm, discrimination due to race/ethnicity) at any time during pregnancy	Maternal reported wheeze and asthma using the ISAAC questionnaire	Maternal anxiety and current asthma: adjusted Moderate vs none: RR 1.22 (0.73-2.05) Somewhat vs none: RR 1.07 (0.67-1.71) Very much vs none: RR 1.39 (0.83-2.35) Maternal chronic stress and current asthma: adjusted Moderate vs low: RR 0.75 (0.49-1.14) High vs low: RR 1.11 (0.67-1.86) Maternal NLEs and current asthma: adjusted 1 NLE vs none: RR 1.21 (0.80-1.83) 2+ NLEs vs none: RR 0.96 (0.58-1.57) Results also given in the paper for ever and current wheeze	Moderate
Bidaki et al 2011; Iran; Prospective cohort study	320	290	At birth	Maternal reported anxiety. Assessed using the Holme-Rahe stress questionnaire at the 3rd trimester of pregnancy	Cord blood IgE	No estimate of effect computed only descriptive data presented in the paper	Moderate
Braig et al 2016; Germany; Prospective cohort study	2,610	787	Up to 2 years	Maternal questionnaire-reported chronic stress, anxiety, and depression symptoms during the 3rd trimester. Also maternal hair cortisol	Maternal questionnaire-reported atopic dermatitis (AD). Dermatologist confirmation using	Maternal chronic stress and AD symptoms: adjusted Quartile 2 vs quartile 1: RR 1.3 (0.8-1.9) Quartile 3 vs quartile 1: RR 1.4 (0.9-2.1) Quartile 4 vs quartile 1: RR 1.5 (1.0-2.3) Maternal depression and AD symptoms : adjusted High vs low: RR 1.4 (1.0-2.0)	Moderate

					SCORAD	Maternal anxiety and AD symptoms: adjusted Quartile 2 vs quartile 1: RR 1.4 (0.9-2.1) Quartile 3 vs quartile 1: RR 1.4 (0.9-2.2) Quartile 4 vs quartile 1: RR 1.5 (0.9-2.4) Maternal hair cortisol and AD symptoms: adjusted Quartile 2 vs quartile 1: RR 1.0 (0.7-1.5) Quartile 3 vs quartile 1: RR 0.9 (0.6-1.4) Quartile 4 vs quartile 1: RR 0.8 (0.5-1.2) Results also given in the paper for parent-reported, paediatrician-reported and strictly defined AD	
Chang et al 2016; South Korea; Prospective cohort study	Cohort 1: 2,021 Cohort 2: 2,150	Cohort 1: 973 Cohort 2: 1,531	Up to 5 years	Maternal questionnaire-reported stress: Cohort 1: depression and anxiety at 3rd trimester Cohort 2: depression any time during pregnancy	AD symptoms Cohort 1: diagnosis by pediatric allergist Cohort 2: maternal report using ISAAC questionnaire	Cohort 1: maternal depression and AD: adjusted HR 1.31 (1.02-1.69) Cohort 1: maternal anxiety and AD: adjusted HR 1.41 (1.06-1.89) Cohort 2: maternal depression and AD: adjusted OR 1.85 (1.06-3.25)	Moderate
Cheng et al 2015; Singapore; Prospective cohort study	1,152	1,067	Up to 1 year	Maternal questionnaire-reported depression (using Edinburgh Postnatal Depression Scale) and anxiety (State-Trait Anxiety Inventory) during 2nd trimester	Maternal reported doctor-diagnosed wheeze, allergic rhinitis, and atopic eczema	Maternal depression: adjusted Wheeze: OR 2.09 (1.05-4.19) Allergic rhinitis: OR 1.13 (0.54-2.36) Atopic eczema: OR 1.13 (0.43- 2.99) Maternal anxiety state: adjusted Wheeze: OR 1.01 (0.63-1.61) Allergic rhinitis: OR 1.82 (1.17-2.82) Atopic eczema: OR 1.01 (0.56-1.81) Maternal anxiety trait: adjusted Wheeze: OR 1.23 (0.78-1.94) Allergic rhinitis: OR 1.70 (1.10-2.61) Atopic eczema: OR 1.02 (0.58-1.81)	Moderate
Chiu et al 2012; Chiu et al 2014; USA; Prospective cohort study	989	653 for Chiu 2012 ; 708 for Chiu 2014	Up to 2 years	Maternal reported 11 domains of NLEs – e.g. financial, relationships, violence, other housing issues, and discrimination and prejudice; exposure to community violence (ECV). Assessed through self-report at 3rd trimester	Maternal questionnaire-reported wheeze in the offspring up to 2 years of age	NLEs and wheeze: adjusted 1-2 vs none: OR 1.95 (0.76-5.00) 3-4 vs none: OR 3.55 (1.38-9.15) 5+ vs none: OR 3.79 (1.39-10.3) ECVs scores and wheeze: adjusted Medium vs low: OR 1.34 (0.71-2.52) High vs low: OR 1.95 (1.13-3.36)	Moderate
Cookson et al 2009; UK; Prospective cohort study	14,062	5,810	Up to 7.5 years	Maternal anxiety reported using the Crown-Crisp	Maternal questionnaire-	Anxiety at 18 weeks and current asthma: adjusted 2nd vs 1st quart. OR 1.24 (1.00-1.55)	Moderate

				Experimental Index. Assessed at 18 and 32 weeks pregnancy	reported doctor-diagnosed current asthma and consultation for wheeze. Specific IgE sensitisation; and methacholine-based bronchohyper-responsiveness (BHR)	3rd vs 1st quart. OR 1.32 (1.07-1.63) 4th vs 1st quart. OR 1.53 (1.22-1.93) Anxiety at 32 weeks and current asthma: adjusted 2nd vs 1st quart. OR 1.36 (1.09-1.71) 3rd vs 1st quart. OR 1.42 (1.14-1.77) 4th vs 1st quart. OR 1.65 (1.30-2.08) Results also given in the paper for wheeze at 18 and 81 months; atopic and non-atopic asthma, asthma + BHR; BHR, and atopic sensitisation	
de Marco et al 2012; Italy; Cross-sectional study	3,907	3,758	3-14 years (mean 8.5 years)	Maternal NLEs (mourning, loss of own or husband's job, separation, divorce). Self-reported questionnaire. Assessed for events occurring during any trimester	Maternal questionnaire-reported ever asthma, wheeze, atopic eczema, and allergic rhinitis	Exposure to any NLEs: adjusted Asthma: OR 1.71 (1.02-2.89) Wheeze: OR 1.41 (1.03-1.94) Atopic eczema: OR 1.53 (1.11-2.10) Allergic rhinitis: OR 1.75 (1.08-2.84)	Moderate
Fang et al 2011; Sweden; Retrospective cohort study	Cohort 1 (born 2004-2008): 449,363 Cohort 2 (born 1997-2002): 514,261	Cohort 1: 426,334 Cohort 2: 493,813	Cohort 1: up to 4 years Cohort 2: 7-12 years	Maternal bereavement. Assessed from population register. For bereavement ≤1 year before pregnancy and at different trimesters	Cohort 1: incident asthma Cohort 2: current asthma Assessed from disease register	Cohort 1: bereavement and asthma onset :adjusted Any time during pregnancy: HR 1.00 (0.87-1.14) 1st trimester: HR 0.98 (0.76-1.27) 2nd trimester: HR 1.18 (0.94-1.48) 3rd trimester: HR 0.87 (0.70-1.09) Cohort 2: bereavement and current asthma: adjusted Any time during pregnancy: OR 0.99 (0.84-1.17) 1st trimester: OR 1.02 (0.76-1.37) 2nd trimester: OR 0.86 (0.63-1.18) 3rd trimester: OR 1.07 (0.84-1.39) Estimates reported in the paper also separately for boys and girls; also by relative type, and by cause of death	Strong
Guxens et al 2014; Netherlands; Prospective cohort study	8,880	4,848	Up to 6 years	Maternal reported depression and anxiety symptoms during the 2nd trimester	Maternal questionnaire-reported doctor-diagnosed ever asthma at 6 years and wheeze at 4 years	Exposure to anxiety + depression: adjusted Ever asthma: OR 1.45 (0.91-2.31) Early wheeze (≤3 yrs): OR 1.23 (0.89-1.69) Late wheeze (at 4 yrs): OR 1.94 (1.04-3.60) Persistent wheeze (1-4 yrs): OR 2.15 (1.47-3.13) Exposure to depression: adjusted Ever asthma: OR 1.33 (0.82-2.16) Early wheeze (≤3 yrs): OR 1.31 (0.97-1.76) Late wheeze (at 4 yrs): OR 2.04 (1.14-3.64) Persistent wheeze (1-4 yrs): OR 1.84 (1.24-2.72) Exposure to anxiety: adjusted	Moderate

						Ever asthma: OR 1.19 (0.76-1.86) Early wheeze (≤3 yrs): OR 1.17 (0.88-1.55) Late wheeze (at 4 yrs): OR 1.81 (1.05-3.12) Persistent wheeze (1-4 yrs): OR 1.72 (1.22-2.43)	
Hartwig et al 2014; Australia; Prospective cohort study	2,860	994	14 years	Maternal reported 10 NLEs including separation or divorce, marital problems, problems with children, pregnancy problems, experience of involuntary job loss, partner experienced involuntary job loss, money problems, a residential move, death of a close relative, and death of a close friend. Assessed for events occurring ≤18 and 18-34 weeks of pregnancy	Maternal questionnaire reported current asthma, allergic rhinitis, and atopic eczema. At 6 and 14 years Atopic sensitisation also assessed at 6 and 14 years	Exposure to NLEs by 18 weeks: adjusted Asthma at 6 years: 1 vs no NLEs: OR 1.30 (0.86-1.95) 2 vs no NLEs: OR 1.21 (0.72-2.04) 3+ vs no NLEs: OR 1.73 (0.87-3.44) Asthma at 14 years: 1 vs no NLEs: OR 1.12 (0.67-1.87) 2 vs no NLEs: OR 1.08 (0.56-2.07) 3+ vs no NLEs: OR 1.26 (0.54-2.91) Exposure to NLEs by 34 weeks: adjusted Asthma at 6 years: 1 vs no NLEs: OR 1.10 (0.72-1.66) 2 vs no NLEs: OR 1.34 (0.80-2.24) 3+ vs no NLEs: OR 0.99 (0.47-2.08) Asthma at 14 years: 1 vs no NLEs: OR 2.24 (1.33-3.75) 2 vs no NLEs: OR 1.96 (1.01-3.79) 3+ vs no NLEs: OR 1.81 (0.74-4.46) Estimated also reported in the paper for allergic rhinitis, atopic eczema, and atopic sensitisation and by maternal history of asthma	Moderate
Khashan et al 2012; Sweden; Retrospective cohort study	3,290,141	3,193,033	Up to 2-34 years	Bereavement (death of a spouse or child) during the 1st, 2nd and 3rd trimester. Assessed from population register	Asthma hospitalisation and asthma hospitalisation pus other related outcomes (bronchitis, COPD, allergic rhinitis, atopic dermatitis, ALRI). Assessed from national patient register	Death of spouse or child: adjusted Asthma hospitalisation: RR 1.43 (1.06-1.92) Asthma hospitalisation + other related outcomes: RR 1.40 (1.14-1.72) Death of spouse only: adjusted Asthma hospitalisation: RR 1.59 (1.10-2.30) Asthma hospitalisation + other related outcomes: RR 1.64 (1.29-2.10)	Strong
Larsen et al 2014; Denmark; Prospective cohort study	100,418	32,271	Up to 7 years	Psychosocial job strain/stress. Assessed using questionnaire and telephone interviews. Assessed for events	Maternal reported current asthma and atopic dermatitis (AD). Assessed using	Work stress and asthma + AD: adjusted High vs low strain: OR 1.11 (0.88-1.40) Active vs low strain: OR 1-09 (0.95-1.25) Passive vs low strain: OR 1.10 (0.91-1.34)	Moderate

				during 2nd trimester	ISAAC-based questionnaire	Results also given in the paper for having asthma and no AD and for having AD and no asthma	
Lee et al 2016; USA; Prospective cohort study	989	765	Up to 6 years	Maternal questionnaire-reported NLEs in 11 domains (eg, financial, legal, career, relationships, home safety, community safety, medical issues pertaining to self, medical issues pertaining to others, home issues, authority, and prejudice) any time during pregnancy.	Maternal reported clinician-diagnosed asthma	NLEs and asthma onset: adjusted All 1-2 NLEs vs none: OR 1.05 (0.59-1.88) 3-4 NLEs vs none: OR 1.60 (0.88-2.92) ≥5 NLEs vs none: OR 2.02 (1.05-3.87) Continuous: OR 1.31 (1.07-1.60) Boys: Continuous: OR 1.38 (1.06-1.79) Girls: Continuous: OR 1.17 (0.84-1.63) Results also given in paper for mutual adjustment for prenatal and postnatal maternal stress	
Lefevre et al 2011; France; Case-control study	Cases: 142 Controls: 142	Cases: 138 Controls: 109	<2 years	Maternal questionnaire-reported anxiety and depression symptoms occurring any time during pregnancy	Maternal reported wheeze and objective measures of eosinophila and IgE sensitisation	Depression and wheeze: adjusted OR 1.55 (0.12-19.8) Anxiety and wheeze: adjusted OR 1.98 (0.69-5.68)	Moderate
Lin et al 2004; Taiwan; Prospective cohort study	353	334	At birth	Maternal questionnaire-reported stress (comprising nervousness, exhaustion, anxiety, tiredness, working stress, and discouragement) at any time during pregnancy	Cord blood IgE sensitisation	Maternal stress and cord blood IgE sensitisation: adjusted OR 7.7 (1.1- 58.9) Maternal nervousness and cord blood IgE sensitisation: adjusted Occasionally vs never/seldom: OR 1.1 (0.5-2.5) Regularly vs never/seldom: OR 4.0 (1.3-12.8)	Moderate
Liu et al 2015; Denmark; Retrospective cohort study	755,358	733,685	Up to 3 years	Maternal depression and use of antidepressant drugs throughout pregnancy. Assessed from population register	Asthma onset assessed from medication prescription database	Maternal depression vs none: adjusted HR 1.25 (1.20-1.30) Use of antidepressant vs non-use: adjusted HR 1.25 (1.18-1.33)	Strong
Liu et al 2015; Denmark; Retrospective cohort study	755,358	750,058	Up to 15 years	Maternal bereavement throughout pregnancy. Assessed from population register	Asthma onset assessed from medication prescription database	Maternal bereavement vs none: adjusted 0-3 years: HR 1.04 (1.00-1.07) 4-15 years: HR 1.02 (0.96-1.09) Timing of maternal bereavement: adjusted 0-3 years: 1st trimester: HR 1.05 (0.95-1.15); 2nd trimester: HR 0.99 (0.91-1.08); 3rd trimester: HR 1.06	Strong

						(0.96-1.17) 4-15 years: 1st trimester: HR 1.06 (0.89-1.27); 2nd trimester: HR 0.88 (0.74-1.04); 3rd trimester: HR 0.95 (0.77-1.16) Results also given in the paper for type of relative death and cause of death and also stratified by maternal asthma history	
Peters et al 2012; USA; Prospective cohort study	500	403	At birth	Maternal questionnaire-reported NLEs (financial, legal, career, relationships, medical, safety in community and home, difficulty with authority, and discrimination) during 3rd trimester	Total cord blood IgE sensitisation using CAP fluorescent enzyme immunoassay	NLEs score and log cord blood IgE in all women: β 0.10 (0.03-0.16) NLEs score and log cord blood IgE in atopic women: β 0.13 (0.02-0.24) NLEs score and log cord blood IgE in all women: β 0.05 (-0.03-0.14)	Moderate
Polloni et al 2015; Italy; Case-control study	Cases: 67 Controls: not indicated	Cases: 59 Controls: 59	Mean 8.3 years	Maternal questionnaire-reported NLEs: bereavement, divorce or separation, financial problem, and anxiety symptoms at any time during pregnancy	Food allergy assessed via IgE, skin prick test, clinical evaluation	Only descriptive results are given in paper	Weak
Radhakrishnan et al 2016; Canada; Retrospective cohort study	122,333	122,333	12 years	Maternal use of mental health services any time during the 12 months preceding child birth. Assessed from health administrative records	Physician diagnosed asthma based on health administrative records	Maternal stress and asthma: adjusted OR 1.16 (1.12-1.20)	Moderate
Reyes et al 2011; USA; Prospective cohort study	727	279	Up to 5 years	Maternal questionnaire-reported demoralisation during the 3rd trimester	Maternal questionnaire-reported wheeze. Serum total and specific IgE sensitisation to inhalant allergens	Unit increase in maternal demoralisation score: adjusted Any wheeze at 5 yrs: OR 1,66 (1.29-2.14) Transient wheeze (3-30 mo): OR 2.25 (1.34-3.76) Late onset wheeze (>30 mo): OR 1.39 (0.61-3.17) Persistent wheeze (3-5 yrs): OR 2.69 (1.52-4.76) Specific IgE sensitisation: OR 0.96 (0.57-1.60)	Moderate
Rosa et al 2016; Mexico; Prospective cohort study	815	417 Boys: 211 Girls: 206	Up to 4 years	Maternal questionnaire-reported NLEs in 11 domains (financial, legal, career, relationship,	Maternal reported ever and current wheeze using the ISAAC	Unit increase in NLEs scores and ever wheeze: adjusted All: RR 1.08 (1.00-1.16) Boys: RR 1.12 (1.02-1.24)	Moderate

				home safety, neighbourhood safety, medical issues (self and others), home, prejudice, and authority) during the 2nd or 3rd trimester	questionnaire	Girls: RR 1.03 (0.92-1.15) Unit increase in NLEs scores and current wheeze: adjusted All: RR 1.12 (1.00-1.26) Boys: RR 1.11 (0.96-1.28) Girls: RR 1.11 (0.93-1.34)	
Sausenthaler et al 2009; Germany; Prospective cohort study	3097	3004	Up to 6 years	Indicators of psychological, social, and serological stress at any time during pregnancy. Assessed from maternity cards	Maternal questionnaire-reported atopic eczema	Any stress and atopic eczema: adjusted Atopic eczema by 1 year: OR 1.24 (0.72-2.13) Atopic eczema by 2 years: OR 1.48 (0.95-2.30) Atopic eczema by 3 years: OR 1.06 (0.66-1.70) Atopic eczema by 4 years: OR 1.06 (0.67-1.68) Atopic eczema by 5 year: OR 1.21 (0.76-1.91) Atopic eczema by 6 year: OR 1.13 (0.71-1.79)	Moderate
Sternthal et al 2009; USA; Prospective cohort study	500	478	At birth	Maternal questionnaire-reported exposure to interpersonal trauma during the 3rd trimester	Total cord blood IgE sensitisation using CAP fluorescent enzyme immunoassay	Interpersonal trauma vs none: adjusted OR 2.19 (0.89-5.38)	Moderate
Turcotte-Tremblay et al 2014; Canada; Prospective cohort study	224	68	11-12 years	Maternal questionnaire-reported posttraumatic stress disorder occurring at any time during pregnancy	Maternal questionnaire-reported doctor-diagnosed current asthma, use of asthma medication and wheeze	Maternal stress and wheeze: adjusted Girls only: OR 1.11 (1.01-1.23) Girls and boys: OR 0.97 (0.91-1.03) Maternal stress and asthma: adjusted Girls only: OR 1.09 (1.00-1.19) Boys only: OR 0.88 (0.78-0.99) Girls and boys: OR 0.88 (0.78-0.99) Maternal stress and asthma medication: adjusted Girls only: OR 1.12 (1.01-1.25) Girls and boys: OR 0.95 (0.87-1.02)	Moderate
Wang et al 2013; Taiwan; Prospective cohort study	24,200	19,381	Up to 3 years	Maternal questionnaire-reported work stress occurring at any time during pregnancy	Maternal questionnaire-reported parent-perceived and doctor-diagnosed AD	Work stress and parent-perceived AD: adjusted Intermediate vs low/no stress: OR 1.20 (1.00-1.46) High vs low/no stress: OR 1.43 (1.20-1.70) Work stress and doctor-diagnosed AD: adjusted Intermediate vs low/no stress: OR 1.22 (1.05-1.41) High vs low/no stress: OR 1.34 (1.16-1.54)	Moderate
Wen et al 2011; Taiwan; Prospective cohort study	1,264	730	Up to 2 years	Maternal questionnaire-reported indicators of stress (vitality, vigour, happiness, anxiety, discouragement,	Maternal reported AD via telephone	Maternal stress and AD: adjusted Medium vs low/no stress: OR 1.10 (0.40-2.80) High vs low/no stress: OR 2.30 (1.10-5.30)	Moderate

				nervousness, tiredness, exhaustion, and work stress) occurring during the 3rd trimester			
Wood et al 2011; USA; Prospective cohort study	1,850	515	1 year	Maternal questionnaire-reported exposure to work stress, community violence, anxiety, and depression during the 2nd and 3rd trimester	Maternal questionnaire-reported wheeze and atopic eczema. IgE sensitisation	All estimates presented in figures. Higher maternal stress scores appeared associated with increased risk of wheeze and atopic eczema	Moderate
Wright et al 2010; USA; Prospective cohort study	1,853	560	At birth	Maternal questionnaire-reported difficult life circumstances, economic strain, neighbourhood /block conditions, perceived community violence and housing worries.	Cord blood cytokine responses	Only p-values presented in paper, hence results difficult to interpret	Moderate

Table S2: Domain specific quality assessment of studies on the association between maternal psychosocial stress during pregnancy and risk of allergy and asthma in the offspring

Reference; country	Overall risk of bias assessment	Risk of bias assessment for study components				
		Study design	Exposure assessment	Outcome assessment	Selection bias	Confounding
Andersson et al 2016; USA	Moderate	Strong	Moderate	Strong	Moderate	Moderate
Bandoli et al 2016; USA	Moderate	Moderate	Moderate	Moderate	Weak	moderate
Bidaki et al 2011; Iran	Moderate	Strong	Moderate	Strong	Moderate	Weak
Braig et al 2016; Germany	Strong	Strong	Strong	Strong	Moderate	Moderate
Chang et al 2016; South Korea	Moderate	Strong	Moderate	Moderate	Moderate	Moderate
Cheng et al 2015; Singapore	Moderate	Strong	Moderate	Moderate	Moderate	Moderate
Chiu et al 2012; Chiu et al 2014; USA	Moderate	Strong	Moderate	Moderate	Moderate	Moderate
Cookson et al 2009; UK	Moderate	Strong	Moderate	Moderate	Moderate	Moderate
de Marco et al 2012; Italy	Moderate	Weak	Moderate	Moderate	Moderate	Moderate
Fang et al 2011; Sweden	Strong	Strong	Strong	Strong	Moderate	Moderate
Guxens et al 2014; Netherlands	Moderate	Strong	Moderate	Moderate	Moderate	Moderate
Hartwig et al 2014; Australia	Moderate	Strong	Moderate	Moderate	Weak	Moderate
Khashan et al 2012; Sweden	Strong	Strong	Strong	Strong	Moderate	Moderate
Larsen et al 2014; Denmark	Moderate	Strong	Moderate	Moderate	Moderate	Moderate
Lee et al 2016; USA	Moderate	Strong	Moderate	Moderate	Moderate	Moderate
Lefevre et al 2011; France	Moderate	Moderate	Moderate	Moderate	Weak	Moderate
Lin et al 2004; Taiwan	Moderate	Strong	Moderate	Strong	Moderate	Moderate
Liu et al 2015; Liu et al *in press*; Denmark	Strong	Strong	Strong	Strong	Moderate	Moderate

Peters et al 2012; USA	Moderate	Strong	Moderate	Strong	Moderate	Moderate
Polloni et al 2015; Italy	Weak	Moderate	Moderate	Moderate	Weak	Weak
Radhakrishnan et al; Canada	Moderate	Strong	Moderate	Moderate	Moderate	Moderate
Reyes et al 2011; USA	Moderate	Strong	Moderate	Moderate	Weak	Moderate
Rosa et al 2016; Mexico	Moderate	Strong	Moderate	Moderate	Moderate	Moderate
Sausenthaler et al 2009; Germany	Moderate	Strong	Strong	Moderate	Moderate	Moderate
Sternthal et al 2009; USA	Moderate	Strong	Moderate	Strong	Moderate	Moderate
Turcotte-Tremblay et al 2014; Canada	Moderate	Strong	Moderate	Moderate	Weak	Moderate
Wang et al 2013; Taiwan	Moderate	Strong	Moderate	Moderate	Moderate	Moderate
Wen et al 2011; Taiwan	Moderate	Strong	Moderate	Moderate	Moderate	Moderate
Wood et al 2011; USA;	Moderate	Strong	Moderate	Moderate	Moderate	Moderate
Wright et al 2010; USA	Moderate	Strong	Moderate	Strong	Moderate	Moderate

The overall risk assessment was based on the component risk assessments (i.e., on the suitability of the study design for the research question, validity of exposure and outcome assessments, potential for selection bias, adjustment for confounding factors).

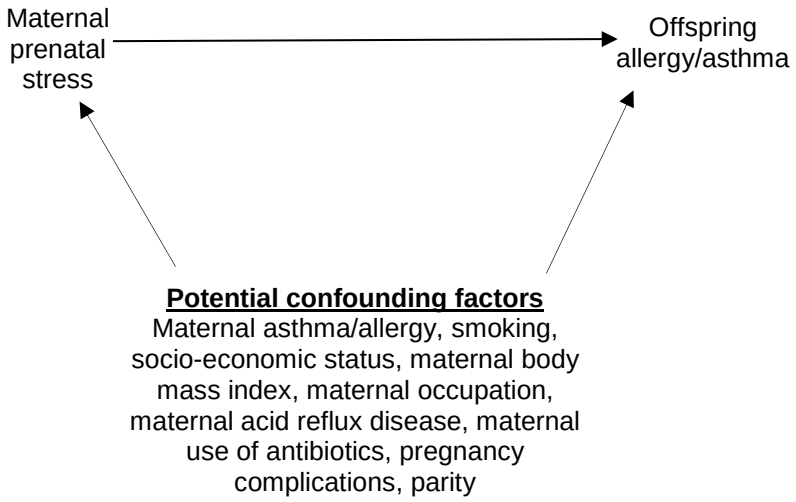


Figure S1 Causal diagram describing the association between maternal prenatal stress and risk of allergy and asthma in the offspring

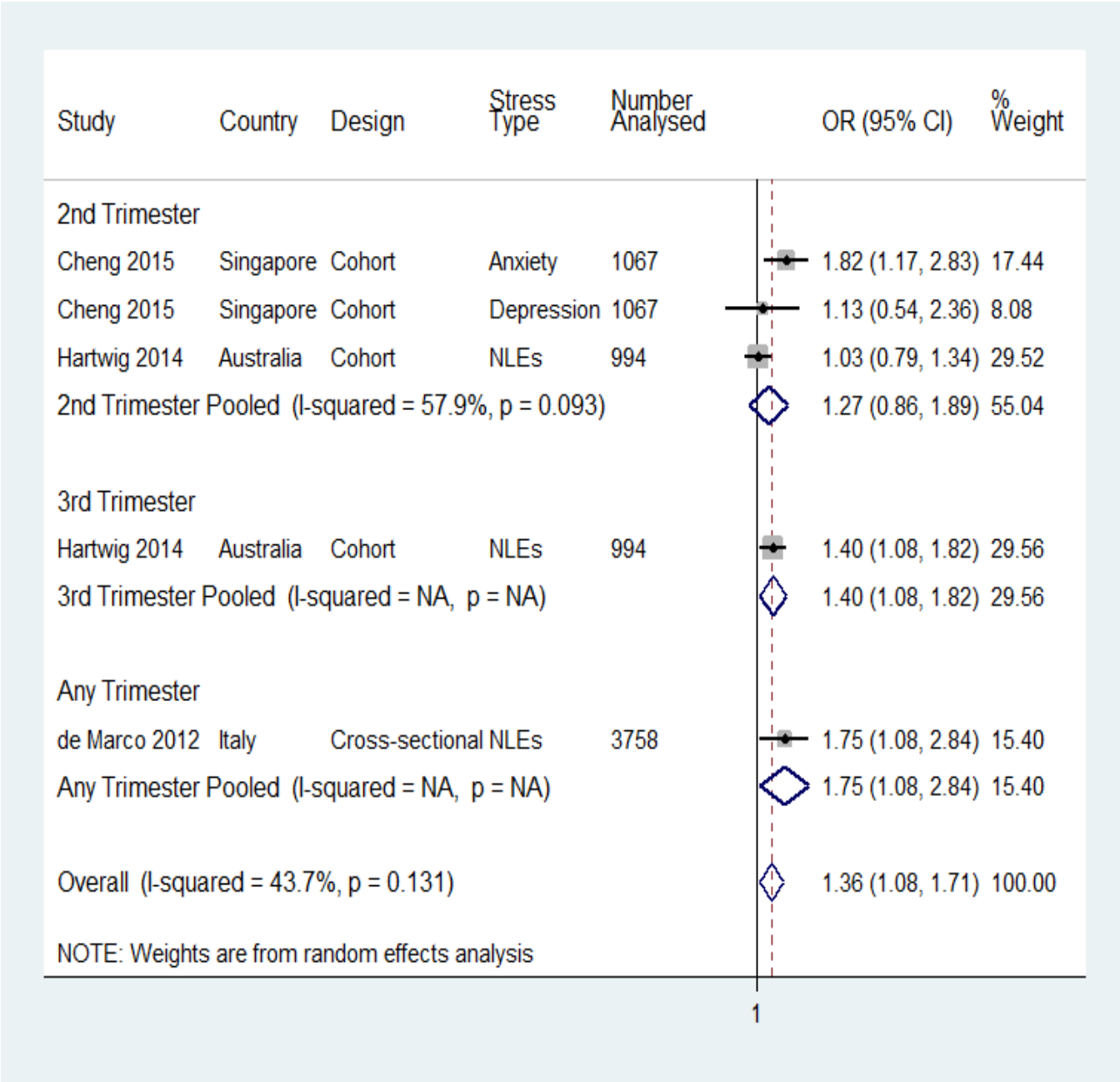


Figure S2. Association between maternal prenatal stress and risk of allergic rhinitis in the offspring, by timing of exposure during pregnancy: No major differences when Hartwig 2014's 6-year-olds and 14-year-olds were analysed separately, hence we presented the results for 14-year-olds

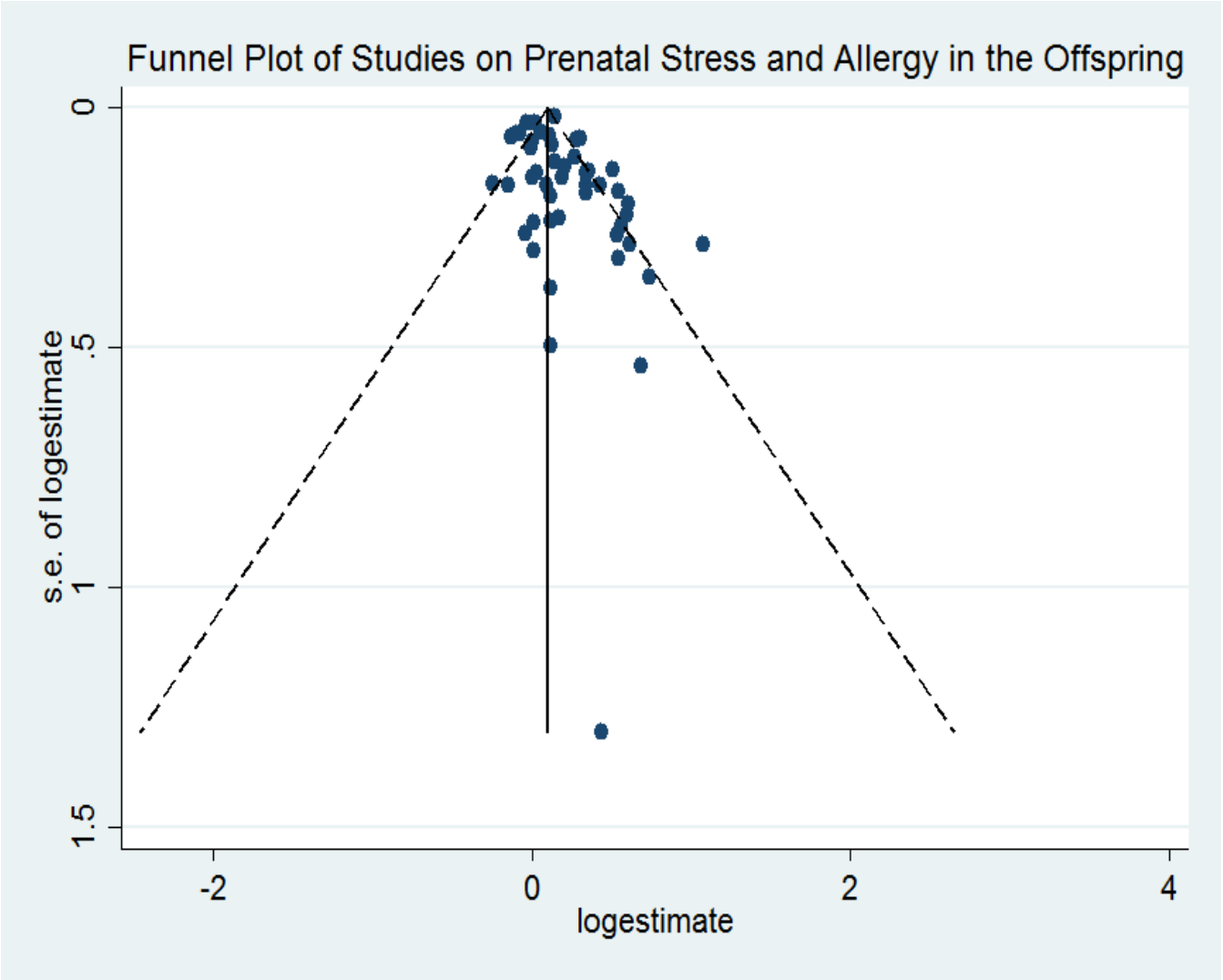


Figure S3. Funnel plot investigating the presence of publication bias or small study effect in studies on the association between maternal prenatal stress and risk of allergy and asthma in the offspring